

(19)

## Europäisches Patentamt

**European Patent Office**

Office européen des brevets



(11)

**EP 1 191 028 A1**

(12)

**EUROPEAN PATENT APPLICATION**

published in accordance with Art. 158(3) EPC

(43) Date of publication:  
**27.03.2002 Bulletin 2002/13**

(21) Application number: 00940912.9

(22) Date of filing: 30.06.2000

(51) Int Cl.7: **C07D 471/20**, C07D 498/10,  
C07D 498/20, C07D 519/00,  
A61K 31/4985, A61K 31/5377,  
A61K 31/541, A61P 7/02,  
A61P 9/00, G01N 33/50,  
G01N 33/15  
// C07M7:00

(86) International application number:  
**PCT/JP00/04374**

(87) International publication number:  
**WO 01/02397 (11.01.2001 Gazette 2001/02)**

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
 MC NL PT SE**  
 Designated Extension States:  
**AL LT LV MK RO SI**

(30) Priority: 30.06.1999 JP 22288399

(71) Applicant: **MOCHIDA PHARMACEUTICAL CO., LTD.**  
**Shinjuku-ku Tokyo 160-8515 (JP)**

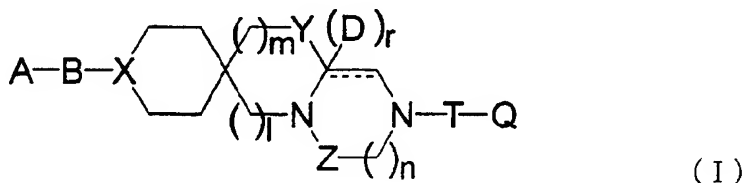
(72) Inventors:  
 • Nishida, Hidemitsu  
 Mochida Pharmaceutical Co., Ltd  
 Tokyo 160-8515 (JP)

- **Saitoh, Fumihiko**  
**Mochida Pharmaceutical Co., Ltd.**  
**Tokyo 160-8515 (JP)**
- **Harada, Kousuke**  
**Mochida Pharmaceutical Co., Ltd.**  
**Tokyo 160-8515 (JP)**
- **Shiromizu, Ikuya**  
**Mochida Pharmaceutical Co., Ltd.**  
**Tokyo 160-8515 (JP)**

(74) Representative: **Grünecker, Kinkeldey,  
Stockmair & Schwanhäusser Anwaltssozietät**  
**Maximilianstrasse 58**  
**80538 München (DE)**

**(54) TRICYCLIC COMPOUNDS HAVING SPIRO UNION**

(57) This invention relates to tricyclic compounds having spiro union represented by the following formula (I) or its salt which is useful as a drug, and in particular, as an inhibitor for activated blood coagulation factor X, which can be administered orally and which exhibits strong anticoagulation action.



The invention also relates to a pharmacophore which was derived from the compound and is useful in molecular designing of the FXa inhibitor.

**EP 1 191 028 A1**

**Description**

## Technical Field

**[0001]** This invention relates to orally administrable tricyclic compounds having spiro union or its salts thereof that are useful as pharmaceuticals, particularly as an inhibitor of activated blood coagulation factor X (hereunder referred to as FXa), and which exhibit potent anticoagulation action.

**[0002]** This invention also relates to a drug designing methods by means of molecular design for creating a compound, which exhibits inhibitory activity for FXa.

## Background Technology

**[0003]** With the westernization of the life style and the increasing number of aged people, ischemic heart diseases and other pathology of heart and blood vessels are increasing year after year. In particular, increase of vascular occlusive diseases such as myocardial infarction, cerebral thrombosis, pulmonary embolism, and peripheral arterial and venous occlusive disease is increasing each year and treatment of such diseases has become a serious social issue. In the treatment and prevention of the thrombosis, anticoagulation therapy has been playing an important role in internal medicine together with anti-platelet therapy and thrombolytic therapy. For the treatment and prevention of thrombosis, safety that permits long-term drug administration and the development of a positive and appropriate anticoagulant activity are essential. Heretofore, anticoagulants such as warfarin and heparin have been used in order to prevent and treat thrombosis due to hypercoagulability. However, such use of the anticoagulants has been pointed to be associated with various demerits including the risk of bleeding and interactions with other drugs. Warfarin is extensively used in the world as the solo peroral anticoagulant. However, due to its characteristics based on the mechanism of action, the concentration range for the development of efficacy is narrow and yet it takes long to develop efficacy and the half-life in blood is as long as 36 hours; what is more, for several reasons such as the great individual difference of effective dose, it is difficult to control the anticoagulability of warfarin (N. Eng. J. Med. 324 (26) 1865-1875, 1991) and frequent monitoring is required in order to prevent bleeding as a side effect. In addition, warfarin also has many other side effects such as nausea, vomiting, diarrhea, and alopecia; thus, warfarin is a drug that involves considerable difficulty in clinical use. On the other hand, heparin is extensively used in the world as an intravenously administrable anticoagulant. However, since it is a direct inhibitor of thrombin, heparin has a high risk of bleeding and needs as frequent monitoring as warfarin; what is more, due to its characteristics based on the mechanism of action, adequate coagulation inhibiting effect is not expected at a lowered antithrombin III level; thus, heparin is a drug that involves considerable difficulty in clinical use. In view of such situation, improved anticoagulants have been desired that has none of the defects inherent in warfarin and heparin.

**[0004]** The blood coagulation cascade is a chain reaction involving limited protein hydrolysis triggered by activation of the extrinsic coagulation cascade or the intrinsic coagulation cascade, and once the cascade is activated, the reaction is amplified like an avalanche. Since the final stage of the blood coagulation cascade is thrombin-mediated conversion of fibrinogen to fibrin, efforts have recently been made to develop thrombin inhibitors; however, drugs that directly inhibit thrombin are known to increase the risk of bleeding. In addition, they have low bioavailability in oral administration; therefore no thrombin inhibitor, which can be orally administered, has been introduced into market.

**[0005]** FXa is a key enzyme, which is located in the upstream of the thrombin in the coagulation cascade, and also at the point of convergence between the extrinsic and the intrinsic coagulation cascade. One molecule of FXa is known to produce about a hundred molecules of thrombin per minute. Therefore, an FXa inhibitor can potentially inhibit the coagulation cascade more efficiently than a thrombin inhibitor (Thrombosis Research, vol. 19, pages 339-349, 1980; Mebio vol. 14, No. 8, 1997).

**[0006]** Compounds that exhibit FXa inhibiting actions have been disclosed in several patents, among which Japanese Patent Application Laid-Opened No.208946/1993 and WO96/16940 disclose aromatic amidine derivatives, and in particular, amidinonaphthyl derivatives, and WO97/38984 and the like disclose cyclic urea compounds having an aminodiphenyl group. However, these compounds are still in the process of development and none have been commercialized to date.

**[0007]** These compounds also suffer from low bioavailability in oral administration, and there is good room of improvement in separating the thrombin inhibitory action and the trypsin inhibitory action from the FXa inhibitory action. In addition, there is apprehension that these compounds are associated with decrease of blood pressure, respiratory insufficiency, and other side effects induced by the amidino group.

**[0008]** With regard to the compound of Japanese Patent Application Laid-Opened No. 208946/1993, use of this compound as a preventive and therapeutic agent for influenza virus is disclosed. The activity of this agent to inhibit the influenza virus propagation is based on the FXa inhibitory action.

**[0009]** Compounds having an aminoheterocyclic group typified by 1-(4-pyridyl)piperidin-4-yl group can be used as

FXa inhibitor; for example, disclosed in prior art references including WO96/10022, WO97/28129, WO97/29104, WO98/21188, WO98/54164, WO99/06371, and WO99/09027.

[0010] These compounds have been developed for the purpose of providing an FXa inhibitor, which is effective in oral absorption. However, low molecular weight FXa inhibitors are still under development and no drug of low molecular weight FXa inhibitors has been commercialized.

[0011] In the development of pharmaceutical products, the desired pharmacological activity is not the sole requirement. Another requirement is that strict criteria be met in various aspects including absorption, distribution, metabolism and excretion, and the like. For example, the drugs are required to pass various examinations for drug interaction, desensitization or tolerance, absorption from digestive tract in the oral administration, transfer rate to small intestine, absorption rate and first pass effect, organ barrier, protein binding, induction of drug metabolizing enzyme, excretion pathway and clearance from body, administration method (site, method, and purpose of administration), and the like, and a drug meeting all such requirements are seldom discovered.

[0012] The anticoagulants also share such general challenge of the drug development.

[0013] In the case of the FXa inhibitor, circumvention of the problem of the side effects associated with the oral administration of the warfarin as well as risk of bleeding based on the thrombin inhibition as found in the case of heparin whose administration is only accomplished by intravenous injection is required.

[0014] When the FXa inhibitor is constructed by molecular designing method, condition of the binding between the FXa and the FXa inhibitor has great significance. In the three-dimensional structure of FXa, active site of the FXa is formed in the structure characteristic to a chymotrypsin-like serine protease.

[0015] The active center of a serine protease is formed from a plurality of pockets called subsites, and it is known that substantially all of the inhibitors which do not form covalent bond with Ser195 residue bind to these pockets. Among such pockets, S1 pocket is believed to be the most important in the serine protease in the binding with the substrate, or in the development of the substrate selectivity.

[0016] S1 site is also believed to be the most important in the serine protease inhibitor for the development of the inhibitory activity and the enzyme selectivity. The residue which is generally believed to be the most important for the substrate specificity in the S1 pocket is the residue corresponding to chymotrypsin No. 189, and FXa has Asp (Asp189) as this residue and the inside of the pocket is believed to be negatively charged.

[0017] However, this is also the case in serine proteases other than the FXa, namely, in trypsin, thrombin, protein C, tissue plasminogen activator, and the like, and such resemblance is one cause of difficulty in enzyme specificity in FXa inhibitor. The substrate specificity of the entire enzyme is determined by structural difference of the subsite such as S3 pocket in addition to the structural difference of S1, and designing of an inhibitor selective for FXa can be accomplished by using such structural difference.

[0018] With regard to the binding state between the FXa and the FXa inhibitor, there has been only the report for specific compounds (DX-9065a and FX-2212a) by X-ray crystallographic analysis.

[0019] In DX-9065a, amidino group is bound to S1 pocket of the FXa, and in particular, Asp189 and the amidino group are firmly bound to each other by electrostatic interaction and hydrogen bonds. This is the binding manner commonly known in trypsin inhibitors and thrombin inhibitors.

[0020] It has also been found out for FX-2212a that the amidino group is bound to the S1 pocket of the FXa by the similar known binding manner (J. Biol. Chem. 1996 Nov. 22; 271(47):29988-92 Brandstetter H. et al., Proc. Natl. Acad. Sci. USA (1998) Jun. 9; 95(12):6630-5 Kamata K. et al.).

[0021] However, DX-9065a and FX-2212a are insufficient in their efficacy in oral administration, and there was also apprehension for the side effects induced by amidino group and guanidino group. In the meanwhile, it has not been even found out for the FXa inhibitors having other structure whether such X-ray crystallographic analysis is possible, and the binding state with the FXa was not at all found out.

[0022] Accordingly, despite the recognition of the usefulness of the amidino group and the guanidino group, there has been no indication as to what structure should be focused in the effort of searching or developing the FXa inhibitor of different type wherein such defects have been improved since no clue has been provided from the information on interaction based on the crystal structure data of such complex of the FXa with known FXa inhibitory compound, and the structural clue has been sincerely awaited.

#### Disclosure of the Invention

[0023] In view of such situation, there is a demand for an anticoagulant drug which exhibits high safety and excellent effectivity, and which is easy to use. To be more specific, there is a high demand for an anticoagulant which can be orally administered to human and other mammals, and in particular, which can be readily used in clinical practice, and which has realized at least one of avoidance of interaction with other drugs, reduced side effects including reduced risk of bleeding, improved dose response, and the like.

[0024] In addition, in the search and development of an FXa inhibitor, there is a high demand for proposal of a

pharmacophore (pharmacophore: parameter in the molecular design which can be used in the discovery of the inhibitor by means of computer-aided drug design) which can be used in the discovery of drugs of the type different from DX-9065a and the like which exhibit same type of bonding as the trypsin inhibitor and the thrombin inhibitor, and which is useful in the association state between the FXa and the FXa inhibitor to give an important indication.

**[0025]** It should be noted that use of such parameter will enable, for example, in the course of discovering the FXa inhibitory compounds which do not have amidino group or guanidino group, computer-aided construction and search of search parameter for the inhibitory compound; conversion into a compound which can serve as a drug comprising a protein substrate for FXa; departure from known skeleton of the FXa inhibitory compounds exhibiting side effects; de novo design based on the novel pharmacophore; and change of the specificity based on the new parameter owned by the inhibitor for serine protease other than FXa; and the like.

**[0026]** The inventors of the present invention conducted an intensive study in order to solve the problems as described above and to provide a compound which has excellent FXa inhibitory action, and found that the compound of formula (I) having spiro skeleton exhibits remarkably excellent FXa inhibitory action. The present invention has been completed on the bases of such finding.

**[0027]** The inventors of the present invention also succeeded in producing the crystal of the complex of the FXa inhibitor of the present invention and the FXa, and found an important pharmacophore useful in discovering the FXa inhibitor of the type which is different from DX-9065a and the like through the analysis of such crystal. The present invention has been completed also on the basis of such finding.

#### Brief Description of the Drawings

##### **[0028]**

FIG. 1 is a view showing structural formulae of the compounds of the present invention.

FIG. 2 is a view showing structural formulae of the compounds of the present invention.

FIG. 3 is a view showing structural formulae of the compounds of the present invention.

FIG. 4 is a view showing structural formulae of the compounds of the present invention.

FIG. 5 is a view showing structural formulae of the compounds of the present invention.

FIG. 6 is a view showing structural formulae of the compounds of the present invention.

FIG. 7 is a view showing structural formulae of the compounds of the present invention.

FIG. 8 is a view showing structural formulae of the compounds of the present invention.

FIG. 9 is a view showing structural formulae of the compounds of the present invention.

FIG. 10 is a view showing structural formulae of the reference compounds B and C.

FIG. 11 is a view showing synthesis route of the compound of the present invention.

FIG. 12 is a view showing synthesis route of the compound of the present invention.

FIG. 13 is a view showing synthesis route of the compound of the present invention.

FIG. 14 is a view showing synthesis route of the compound of the present invention.

FIG. 15 is a view showing synthesis route of the compound of the present invention.

FIG. 16 is a view showing synthesis route of the compound of the present invention.

FIG. 17 is a view showing synthesis route of the compound of the present invention.

FIG. 18 is a view showing synthesis route of the compound of the present invention.

FIG. 19 is a view showing synthesis route of the compound of the present invention.

FIG. 20 is a view showing synthesis route of the compound of the present invention.

FIG. 21 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 22 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 23 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 24 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 25 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 26 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 27 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 28 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 29 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 30 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 31 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 32 is a view showing physical property data (NMR spectrum) of the compounds of the present invention.

FIG. 33 is a view showing physical property data (X ray chart table) of the compounds of the present invention.

FIG. 34 is a view showing physical property data (X ray chart table) of the compounds of the present invention.

FIG. 35 is a view showing physical property data (X ray chart table) of the compounds of the present invention.



FIG. 36 is a view showing physical property data (X ray chart table) of the compounds of the present invention.

FIG. 37 is a ribbon diagram of human FXa (Des-Gla Domain).

FIG. 38 is a ribbon diagram of human FXa (Des-Gla Domain)-Compound A complex.

FIG. 39 is a view showing active site of human FXa.

5 FIG. 40 is a view showing the active site of human FXa-Compound A complex.

FIG. 41 is a stereo view of the active site of human FXa-Compound A complex.

FIG. 42 is a view of the table showing serial Nos. of the residues of serine protease domain of FXa corresponding to the chymotrypsin Nos. in the amino acid sequence of the serine protease domain of FXa.

## 10 Best Embodiments for Carrying Out the Invention

**[0029]** Next, the present invention is described in detail. The present invention relates to a tricyclic compound having spiro union as represented by formula (I) which will be described below, intermediates thereof, and pharmacophores which are useful in molecule design of a FXa inhibitor.

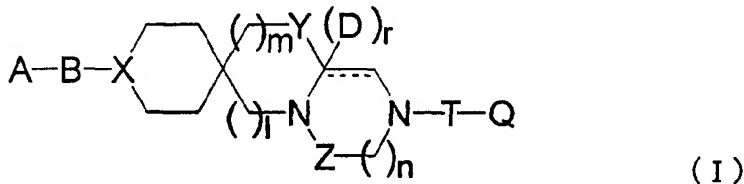
15 **[0030]** Various embodiments of the present invention are described in the following. In the compound of the present invention, "C<sub>1-6</sub>", for example, means that "the group is a straight chain or branched group containing 1 to 6 carbon atoms" unless otherwise noted. In the case of a cyclic group, "C<sub>1-6</sub>" denotes "the number of ring member carbon atoms".

**[0031]** The compound of formula (I) and the compound of formula (I') according to the present invention are not particularly limited for their molecular weight. The molecular weight, however, is preferably up to 1000, and more preferably up to 700 (and otherwise stated, the total number of carbon atoms constituting the compound is less than 40). Such limitation of molecular weight is routinely employed for identifying the structure of the compound as a major limiting factor in addition to the pharmacologically characteristic basic skeleton in recent drug design. In particular, the molecular weight is preferably limited to the range of up to 1000 when oral absorptivity of the drug is taken into consideration.

25 [1] First aspect of the invention

**[0032]** The compound of this invention is represented by formula (I) or its pharmaceutically acceptable salt.

30



35

In the formula,

40

A is a hydrogen atom, or a group selected from (1) a saturated or unsaturated five- or six-membered cyclic hydrocarbon group, or a saturated or unsaturated five- or six-membered heterocyclic group, (2) an amino group, and (3) an imidoyl group (wherein the groups of (1) to (3) are optionally substituted);

45 B is a single bond, a carbonyl group, -S(O)<sub>x</sub>-, or an optionally substituted C<sub>1-2</sub> alkylene group;

D is a hydrogen atom, -CO-R<sub>5</sub> (wherein R<sub>5</sub> is hydrogen atom or a substituent), or an optionally substituted C<sub>1-6</sub> alkyl group;

X is a nitrogen atom or a methine group optionally substituted with group A'-B' (wherein A' represents a group selected from those defined for A, and B' represents a group selected from those defined for B);

50 Y is an oxygen atom, -S(O)<sub>y</sub>-, or an optionally substituted imino group (-NH-);

Z is a methylene group, a carbonyl group, or a thiocarbonyl group;

T is -S(O)<sub>2</sub>-, a carbonyl group, or an optionally substituted C<sub>1-2</sub> alkylene group;

Q is a hydrocarbon group or a heterocyclic group, which are optionally substituted;

55 I, m, n, x, y, and z are independently an integer selected from 0, 1 and 2 with the proviso that I and m are not simultaneously 0; and r is an integer of 0 or 1; and

the three rings (the ring containing X, the ring containing Y, and the ring containing Z) are independently optionally substituted; and the bond indicated by the broken line and the solid line in the ring containing Z is single bond or double bond (when r is 0).

**[0033]** Various groups included in the formula (I) are described in detail.

[1-1] In the compound of formula (I), Q is a hydrocarbon group or a heterocyclic group, and these groups may optionally have substituents. Exemplary "hydrocarbon groups" within the definition of Q include aliphatic hydrocarbon groups, alicyclic hydrocarbon groups, and aryl groups, and the preferred is an aryl group.

**[0034]** Exemplary "aliphatic hydrocarbon groups" include straight- or branched-chain hydrocarbon groups, for example, alkyl groups, alkenyl groups, alkynyl groups, and the like.

**[0035]** Exemplary "alkyl groups" include C<sub>1-10</sub> (and more preferably C<sub>1-6</sub>) alkyl groups, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, n-hexyl, 1-methyl-heptyl, and n-nonyl.

**[0036]** Exemplary "alkenyl groups" include C<sub>2-6</sub> alkenyl groups, for example, vinyl, allyl, isopropenyl, 2-methylallyl, butenyl, pentenyl, and hexenyl.

**[0037]** Exemplary "alkynyl groups" include C<sub>2-6</sub> alkynyl groups, for example, ethynyl, 1-propynyl, 2-propynyl, butynyl, pentynyl, and hexynyl.

**[0038]** Exemplary "alicyclic hydrocarbon groups" include saturated and unsaturated alicyclic hydrocarbon groups, for example, cycloalkyl group, cycloalkenyl group, and cycloalkanedieryl group.

**[0039]** Exemplary "cycloalkyl groups" include C<sub>3-9</sub> cycloalkyl groups, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl.

**[0040]** Exemplary "cycloalkenyl groups" include C<sub>3-6</sub> cycloalkenyl groups, for example, 1-cyclopropen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, and 1-cyclohexen-1-yl.

**[0041]** Exemplary "cycloalkanedieryl groups" include C<sub>4-6</sub> cycloalkanedieryl groups, for example, 2,4-cyclopentadien-1-yl and 2,5-cyclohexadien-1-yl.

**[0042]** Exemplary "aryl groups" include C<sub>6-14</sub> aryl groups, for example, phenyl, naphthyl, biphenyl, 2-anthryl, phenanthryl, acenaphthyl, and 5,6,7,8-tetrahydronaphthalenyl(2-yl), and among these, the preferred are phenyl, 2-naphthyl, and 1-naphthyl.

**[0043]** Exemplary heterocyclic groups of the "optionally substituted heterocyclic groups" in Q include aromatic heterocyclic groups, and saturated and unsaturated non-aromatic heterocyclic groups. Exemplary such heterocyclic groups include those having a five- to fourteen-membered ring, and preferably, a five- to twelve-membered ring containing at least one heteroatom (preferably 1 to 4 heteroatoms) selected from N, O and S in addition to the carbon atoms.

**[0044]** Exemplary "aromatic heterocyclic groups" include monocyclic and fused heterocyclic groups. Preferable monocyclic aromatic heterocyclic groups are those containing 5 to 6 ring members, for example, pyrrolyl, furyl, thienyl, oxazolyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,2,5-triazinyl, 1,3,5-triazinyl, and thiadiazinyl.

**[0045]** Preferable fused aromatic heterocyclic groups are those containing 8 to 12 ring members, for example, monovalent groups formed by condensation of the five- or six-membered aromatic ring as described above with 1 or a plurality of (preferably 1 to 2) aromatic rings (for example, benzene ring) followed by removal of hydrogen atom at an arbitrary position from the thus formed ring.

**[0046]** Exemplary such groups include indolyl, isoindolyl, 1H-indazolyl, benzofuranyl (-2-yl), isobenzofuranyl, benzothienyl (-2-yl), isobenzothienyl, benzindazolyl, benzoxazolyl (-2-yl), 1,2-benzisoxazolyl, benzothiazolyl (-2-yl), 1,2-benzisothiazolyl, 2H-benzopyranyl (-3-yl), (1H)-benzimidazolyl (-2-yl), 1H-benzotriazolyl, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, quinolyl, isoquinolyl, cinnolyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyliziny, purinyl, pteridinyl, carbazolyl, carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxazinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indoliziny, (4,5,6,7-) tetrahydrothiazolo[5,4-c]pyridyl (-2-yl), (4,5,6,7-) tetrahydrothieno[3,2-c]pyridyl, (1,2,3,4-) tetrahydroisoquinolyl (-6-yl), thiazolo[5,4-c]pyridyl (-2-yl), pyrolo[1,2-b]pyridazinyl, pyrazo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,5-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl (Preferred embodiments are indicated in the bracket).

**[0047]** Exemplary "non-aromatic heterocyclic groups" include three- to eight-membered saturated and unsaturated non-aromatic heterocyclic groups, for example, azetidyl, oxilanyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, pyrazolinyl, pyrazolidinyl, pyperidyl, tetrahydropyranyl, pyperadinyl, morpholinyl, thiomorpholinyl, and quinucidinyl.

**[0048]** Exemplary "substituents" of the "optionally substituted hydrocarbon group" or the "optionally substituted heterocyclic group" in Q include (a) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and cycloalkenyl, (b) heterocyclic groups, (c) amino, (d) imido, (e) hydroxyl, thiol, and oxo, (e) halogen atoms such as fluorine, chlorine, bromine, and iodine, cyano, and nitro, (f) carboxyl, and (g) carbamoyl, thiocarbamoyl, sulfonyl, sulfinyl, sulfide and acyl. Of the (a) to (g) as

described above, the groups excluding (e) may further comprise a substituent.

**[0049]** The "optionally substituted hydrocarbon group" and the "optionally substituted heterocyclic group" in Q may be arbitrarily substituted with 1 to 5 such substituents. Such substituents (a) to (f) are described in further detail.

(a) The alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and cycloalkenyl groups may be any of the "alkyl groups", "alkenyl groups", "alkynyl groups", "aryl groups", "cycloalkyl groups" and "cycloalkenyl groups" mentioned as examples of the "hydrocarbon group" for Q, and the preferred are C<sub>1-6</sub> alkyl groups, C<sub>2-6</sub> alkenyl groups, C<sub>2-6</sub> alkynyl groups, C<sub>6-14</sub> aryl groups, C<sub>3-7</sub> cycloalkyl groups and C<sub>3-6</sub> cycloalkenyl groups.

These groups may further include an optional substituent RI (wherein RI represents a group selected from C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkoxycarbonyl, carboxyl, carbamoyl which is optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> alkyl, halogenated C<sub>1-6</sub> alkyl, amino which is optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenylamino, nitro, hydroxyl, oxo, cyano, and amidino).

(b) The heterocyclic group may be any of the "aromatic heterocyclic groups" and "non-aromatic heterocyclic groups" mentioned as examples of the "heterocyclic group" for Q, and the preferred are (i) "five- or six-membered, monocyclic aromatic heterocyclic groups", (ii) "eight- to twelve-membered, fused, aromatic heterocyclic groups", and (iii) "three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic groups", which contain 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom in addition to the carbon atoms.

These groups may further include an optional substituent RII (wherein RII represents a group selected from C<sub>1-6</sub> alkyl groups, C<sub>1-6</sub> alkanoyl groups, and benzoyl group).

(c) The "optionally substituted amino group" may be, for example, amino group which is optionally mono- or di-substituted with substituent RIII (wherein RIII represents a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl, C<sub>2-6</sub> alkenoyl, benzoyl, and C<sub>1-6</sub> alkoxycarbonyl which is optionally substituted with 1 to 5 halogen atoms), or three- to eight-membered monocyclic amino group which is optionally substituted with a group selected from C<sub>1-6</sub> alkyl, C<sub>7-10</sub> aralkyl and C<sub>6-10</sub> aryl.

(d) Exemplary substituents in the "optionally substituted imido group, the optionally substituted amidino group, the optionally substituted hydroxyl group, and the optionally substituted thiol group" include RIII (RIII represents a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl, C<sub>2-6</sub> alkenoyl, benzoyl, and C<sub>1-6</sub> alkoxycarbonyl which is optionally substituted with 1 to 5 halogen atoms) described in (c). Therefore, examples of (d) include C<sub>1-6</sub> alkylimido groups, formimido group or amidino group, benzyloxy group, C<sub>1-6</sub> alkanoyloxy groups, and oxo group.

(e) Halogen atoms such as fluorine, chlorine, bromine, and iodine, cyano group, and nitro group.

(f) The "optionally substituted carboxyl groups" include carboxyl group, C<sub>1-6</sub> alkoxycarbonyl groups, C<sub>7-12</sub> aryloxy-carbonyl groups, and C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkoxycarbonyl groups, and the aryl group in such (f) is optionally substituted with substituent RIV. RIV represents amino group which is mono- or di-substituted with substituent RII (wherein RII represents a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, or benzoyl group) of (b); halogen atom; hydroxyl group; nitro group; cyano group; a C<sub>1-6</sub> alkyl group which is optionally substituted with 1 to 5 halogen atoms; or an alkoxy group which is optionally substituted with 1 to 5 halogen atoms.

(g) The "optionally substituted carbamoyl group, the optionally substituted thiocarbamoyl group, the optionally substituted sulfonyl, the optionally substituted sulfinyl, the optionally substituted sulfide and the optionally substituted acyl group" are, for example, the groups represented by -CONRgRg', -CSNRgRg', -SO<sub>y</sub>-Rg, or -CO-Rg, wherein:

Rg represents hydrogen atom or substituent RV (wherein RV represents C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, C<sub>7-10</sub> aralkyl, or a heterocyclic group, and the heterocyclic group is a heterocyclic group containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom in addition to the carbon atoms which is any one of (i) a five- or six-membered monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered fused aromatic heterocyclic group, and (iii) a three- to eight-membered saturated or unsaturated non-aromatic heterocyclic group, and the alkyl, the cycloalkyl, the aryl, the aralkyl, or the heterocyclic group is optionally further substituted with substituent RIV of (f));

Rg' is hydrogen atom or a group selected from C<sub>1-6</sub> alkyl groups, C<sub>3-6</sub> cycloalkyl groups, and C<sub>7-10</sub> aralkyl groups; and

y is 0, 1, or 2.

**[0050]** In the compound of the formula (I), Q is preferably as described below.

[1-1-a] Examples of the "optionally substituted hydrocarbon group" or the "optionally substituted heterocyclic group" include:

(1) C<sub>1-10</sub> alkyl groups; (2) C<sub>2-6</sub> alkenyl groups; (3) C<sub>2-6</sub> alkynyl groups; (4) C<sub>3-9</sub> cycloalkyl groups; (5) C<sub>3-6</sub> cycloalkenyl groups; (6) C<sub>4-6</sub> cycloalkanedienyl groups; (7) C<sub>6-14</sub> aryl groups; and (8) (i) "five- or six-membered, monocyclic aromatic heterocyclic groups", (ii) "eight- to twelve-membered, fused aromatic heterocyclic groups", and (iii) "three- to eight-

membered, saturated or unsaturated, non-aromatic heterocyclic groups", which contain 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom in addition to the carbon atoms, and each group of the above (1) to (8) may be either unsubstituted or substituted with 1 to 5 substituents of the class selected from (a-1) to (g-1) as described below.

**[0051]** The classes are:

(a-1): C<sub>1-6</sub> alkyl groups, C<sub>2-6</sub> alkenyl groups, C<sub>2-6</sub> alkynyl groups, C<sub>6-14</sub> aryl groups, C<sub>3-7</sub> cycloalkyl groups, and C<sub>3-6</sub> cycloalkenyl groups. These substituents are optionally further substituted with substituent RI (wherein RI represents a group selected from C<sub>1-6</sub> alkoxy; C<sub>1-6</sub> alkoxy-carbonyl; carboxyl; carbamoyl which is optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl; a halogen; C<sub>1-6</sub> alkyl; halogenated C<sub>1-6</sub> alkyl; amino which is optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl; C<sub>2-6</sub> alkenoylamino; nitro; hydroxy; oxo; cyano; and amidino).

(b-1): a heterocyclic group containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom in addition to the carbon atoms which is any one of (i) a "five- or six-membered, monocyclic aromatic heterocyclic group", (ii) an "eight- to twelve-membered, fused aromatic heterocyclic group", and (iii) a "three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group". These heterocyclic groups are optionally further substituted with RII (wherein RII represents a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl, and benzoyl).

(c-1): an amino group which is optionally substituted with substituent RIII (wherein RIII represents a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl, C<sub>2-6</sub> alkenoyl, benzoyl, and C<sub>1-6</sub> alkoxy-carbonyl which is optionally substituted with 1 to 5 halogen atoms), and a three- to eight-membered monocyclic amino group which is optionally substituted with a group selected from C<sub>1-6</sub> alkyl, C<sub>7-10</sub> aralkyl and C<sub>6-10</sub> aryl. (d-1): an imido group, an amidino group, a hydroxyl group, and a thiol group. These substituents are optionally substituted with groups selected from substituents RIII as described above in the (c-1).

(e-1): a halogen atom such as fluorine, chlorine, bromine, and iodine, a cyano group, and a nitro group.

(f-1): a carboxyl group, a C<sub>1-6</sub> alkoxy-carbonyl group, a C<sub>7-12</sub> aryloxy-carbonyl group and a C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkoxy-carbonyl group; and the aryl group in such (f-1) is optionally substituted with substituent RIV' (wherein RIV' represents amino which is optionally mono- or di-substituted with groups selected from RIII as described above in the (c-1); C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy which is optionally substituted with 1 to 5 halogen atoms; a halogen atom; hydroxyl; nitro; and cyano).

(g-1): a group -CONRgRg', -CSNRgRg', -CO-Rg and -SO<sub>y</sub>-Rg wherein:

Rg represents a hydrogen atom or a substituent RV (wherein RV represents C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl, C<sub>7-10</sub> aralkyl, or a heterocyclic group, and the heterocyclic group is a heterocyclic group containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom, and nitrogen atom in addition to the carbon atoms which is any one of (i) a five- or six-membered monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered fused aromatic heterocyclic group, and (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group, and the alkyl, the cycloalkyl, the aryl, the aralkyl, or the heterocyclic group is optionally further substituted with substituent RIV as described in the (f-1));

Rg' is a hydrogen atom or a group selected from C<sub>1-6</sub> alkyl groups, C<sub>3-6</sub> cycloalkyl groups, and C<sub>7-10</sub> aralkyl groups; and

y is 0, 1, or 2.

**[0052]** In the groups shown in (a-1) to (g-1) as described above, the "most preferable groups" are substituents including C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen atom, halogenated C<sub>1-6</sub> alkyl, cyano, amino, hydroxyl, carbamoyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkenyloxy, C<sub>2-6</sub> alkynyloxy, C<sub>1-6</sub> alkylthio, C<sub>1-6</sub> alkylsulfinyl, C<sub>1-6</sub> alkylsulfonyl, mono/di C<sub>1-6</sub> alkylamino, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>2-6</sub> alkanoyl, C<sub>2-6</sub> alkanoylamino, hydroxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkyl, carboxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy-carbonyl-C<sub>1-6</sub> alkyl, carbamoyl-C<sub>1-6</sub> alkyl, N-(C<sub>1-6</sub>)alkylcarbamoyl-C<sub>1-6</sub> alkyl, N,N-di C<sub>1-6</sub> alkylcarbamoyl-C<sub>1-6</sub> alkyl, phenyl, phenoxy, phenylthio, phenylsulfinyl, phenylsulfonyl, benzyl, and benzoyl, and the aromatic ring in these substituents may be substituted with 1 to 3 substituents selected from halogen atoms, trifluoromethyl, cyano, hydroxyl, amino, nitro, carboxyl, carbamoyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, mono/di C<sub>1-6</sub> alkylamino, di-C<sub>1-6</sub> alkylcarbamoyl, C<sub>1-6</sub> alkoxy-carbonyl, N-C<sub>1-6</sub> alkylcarbamoyl, N,N-di C<sub>1-6</sub> alkylcarbamoyl, and C<sub>2-6</sub> alkenoylamino.

[1-1-b] Preferably, Q is (1) a C<sub>1-6</sub> alkyl group, (2) a C<sub>2-6</sub> alkenyl group, (7) a C<sub>6-14</sub> aryl group, or (8) (i) a five- or six-membered, monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered, fused aromatic heterocyclic group, or (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group, which contains 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom in addition to the carbon atoms, and each group in (1), (2), (7) and (8) is optionally mono- or di-substituted at an arbitrary position with the substituent of the class selected from [1-1] (a-1) to (g-1) (and most preferably, from those listed as "particularly preferable groups").

[1-1-c] More preferably, Q is (1') or (2'): a C<sub>1-6</sub> alkyl group (most preferably a C<sub>1-2</sub> alkyl group) or a C<sub>2-6</sub> alkenyl group (most preferably a C<sub>2</sub> alkenyl group) substituted with a substituent selected from substituent (a-1): a C<sub>6-14</sub> aryl group

and substituent (b-1): an aromatic group selected from (i) five- or six-membered monocyclic aromatic heterocyclic groups and (ii) eight- to twelve-membered fused aromatic heterocyclic groups, which contain 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom in addition to the carbon atoms; or

(7'): a C<sub>6-14</sub> aryl group which is optionally substituted with 1 to 2 halogen atoms; or (8'): a heterocyclic group which is (i) a five- or six-membered, monocyclic, aromatic heterocyclic group, (ii) an eight- to twelve-membered, fused aromatic heterocyclic group, or (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group, which contains 1 to 4 heteroatoms selected from nitrogen atom, oxygen atom and sulfur atom in addition to the carbon atoms, and wherein the carbon atoms are mono- or di-substituted with a halogen atom.

**[0053]** The aromatic ring in the above substituent (1') or (2') is optionally substituted with 1 to 3 substituents selected from halogen atoms, trifluoromethyl, cyano, hydroxyl, amino, nitro, carboxyl, carbamoyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, mono/di C<sub>1-6</sub> alkylamino, di C<sub>1-6</sub> alkylcarbamoyl, C<sub>1-6</sub> alkoxy carbonyl, N-C<sub>1-6</sub> alkylcarbamoyl, N,N-di 1-6 alkylcarbamoyl and C<sub>2-6</sub> alkenoylamino.

**[0054]** The aromatic ring in the substituents (7') and (8') is also optionally mono- or di-substituted at arbitrary position with the substituent of the class selected from [1-1] (a-1) to (g-1) (and most preferably, from those listed as "particularly preferable groups").

[1-1-d] Still more preferably, Q is benzyl group, phenethyl group, styryl group, 1-naphthyl group, 2-naphthyl group, benzofuran-2-yl group, benzo[b]thien-2-yl group, indolyl-2-yl group, quinolin-3-yl group, 1H-benzimidazol-2-yl group, benzoxazol-2-yl group, benzothiazol-2-yl group, 2H-benzopyran-3-yl group, 4-vinylphenyl group, 4-benzenesulfonylthiophen-2-yl group, or 5-(2-pyridyl)thiophen-2-yl group, and the aromatic ring in such group is optionally mono- or di-substituted with halogen atom (most preferably chlorine atom or bromine atom) or a C<sub>1-6</sub> alkyl group (most preferably methyl group).

[1-2] In the compound of formula (I), A is hydrogen atom; or

(1) an optionally substituted, saturated or unsaturated, five- or six-membered, cyclic hydrocarbon group, or an optionally substituted, saturated or unsaturated, five- or six-membered, heterocyclic group,

(2) an optionally substituted amino group, or

(3) an optionally substituted imido group.

[1-2-a] In the (1) optionally substituted, saturated or unsaturated, five- or six-membered, cyclic hydrocarbon group, or optionally substituted, saturated or unsaturated, five- or six-membered, heterocyclic group,

the "saturated or unsaturated, five- or six-membered, cyclic hydrocarbon group" corresponds to those containing 5 or 6 carbon atoms in the cyclic hydrocarbon groups listed as "alicyclic hydrocarbon groups" and "aryl groups" in Q. Examples are cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclopentadienyl, cyclohexadienyl, and phenyl.

**[0055]** Exemplary "saturated or unsaturated, five- or six-membered, heterocyclic groups" are five- or six-membered, monocyclic groups in the heterocyclic groups shown in "aromatic heterocyclic groups, and saturated or unsaturated, non-aromatic heterocyclic groups" in Q. The heterocyclic groups contain at least one (and preferably 1 to 4) heteroatom selected from N, O, and S in addition to the carbon atoms.

**[0056]** To be more specific, exemplary "non-aromatic heterocyclic groups" include azetidyl, oxilanyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, pyrazolyl, pyrazolidinyl, piperidyl, tetrahydropyranyl, piperidinyl, morpholinyl, thiomorpholinyl, and quinuclidinyl, and

exemplary "aromatic heterocyclic groups" include pyrolyl, furyl, thienyl, oxazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,2,5-triazinyl, 1,3,5-triazinyl, and thiadiazinyl.

**[0057]** The ring in A is optionally further substituted with 1 to 3 substituents R<sub>q</sub> (wherein R<sub>q</sub> is any of substituents (1) to (8) of Q which is optionally substituted with any of substituents (a) to (f)). Alternatively, the ring in A is optionally mono- or di-substituted with a group selected from:

R<sub>1</sub> (wherein R<sub>1</sub> is any group selected from group A (hydrogen atom, halogen atoms, trifluoromethyl group, trifluoromethoxy group, carboxyl group, carbamoyl group, sulfamoyl group, amino group, cyano group, nitro group, lower alkanoyl groups, lower alkoxy groups, lower alkoxy carbonyl groups, lower alkylsulfonyl groups, lower alkylsulfinyl groups, mono- or di-substituted lower alkylamino groups, cyclic amino groups, lower alkanoylamino groups, phenyl group, phenoxy group, benzyloxy group, benzoyl group, mercapto group, lower alkylthio groups, lower alkylthiocarbonyl groups, hydroxy group, and mono- or di-substituted lower alkylamino carbonyl groups); oxygen atom which forms N-oxide group with a cyclic nitrogen atom; and lower alkyl groups, lower alkoxy groups, lower alkenyl groups, phenyl group, five- or six-membered heterocyclic groups which are optionally substituted at an arbitrary number of positions with the substituent of group A).

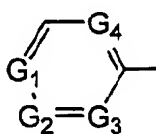
[1-2-b] Examples of the optionally substituted amino group of (2) are amino groups optionally mono- or di-substituted with substituent RVII (wherein RVII is a C<sub>1-10</sub> alkyl group, a formimide group, an acetimidoyl group, a C<sub>2-6</sub> alkenyl group, a C<sub>3-6</sub> cycloalkenyl group, a C<sub>3-9</sub> cycloalkyl group, a C<sub>4-6</sub> cycloalkanedienyl group, or a C<sub>6-14</sub> aryl group). It should be noted that the cyclic amino group is included within the "saturated or unsaturated, five- or six-membered heterocyclic groups" of [1-2-a](1).

[1-2-c] Examples of the optionally substituted imidoyl group of (3) include group: -C(RVII')=N-RVII"

(wherein RVII' and RVII" are the same or different and arbitrarily selected from a hydrogen atom and the substituent RVII as described above in (2)).

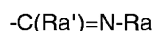
**[0058]** It should be noted that the cyclic imidoyl group is included within [1-2-a] (1) "unsaturated, five- or six-membered, heterocyclic groups".

**[0059]** More preferably, A is a hydrogen atom; or [1-2-a1] a five-membered, aromatic, monocyclic heterocyclic group which may contain 1 to 4 nitrogen atoms or 1 to 3 oxygen atoms or sulfur atoms in addition to the carbon atoms, or the following group:



wherein G<sub>1</sub>, G<sub>2</sub>, G<sub>3</sub>, and G<sub>4</sub> are independently CH or N, and all rings are optionally mono- or di-substituted with any of the (a) to (g) as described above;

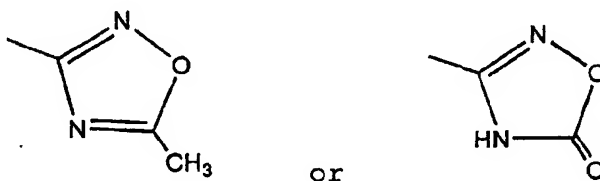
[1-2-b1] an amino group which is optionally mono- or di-substituted with a C<sub>1-10</sub> alkyl group or a C<sub>6-14</sub> aryl group, a formimidoyl-amino group, or an acetimidoyl amino group; or [1-2-c1] group: -N(Ra'')-C(Ra')=N-Ra or group:



(wherein, in each group, Ra'' is a hydrogen atom or a C<sub>1-6</sub> alkyl group;

Ra' is a hydrogen atom; a C<sub>1-6</sub> alkyl group; a C<sub>1-6</sub> alkanoyl group; a benzoyl group; an amino group which is optionally mono- or di-substituted with a group selected from a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkanoyl or a benzoyl; or a C<sub>1-6</sub> alkoxy group; and

Ra is a hydrogen atom, a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, or benzoyl group), or alternatively, -C(Ra')=N-Ra moiety in each group may form:



[1-3] In the compound of formula (I), B is

[1-3-a] a single bond, a carbonyl group, -S(O)<sub>x</sub>- (wherein x is typically 0 to 2, and preferably 2), or an optionally substituted C<sub>1-2</sub> alkylene group (which is typically substituted with an optionally halogenated C<sub>1-6</sub> alkyl group or an optionally halogenated C<sub>1-6</sub> alkoxy group),

[1-3-b] preferably a single bond, a carbonyl group, or -SO<sub>2</sub>-, and

[1-3-c] more preferably a single bond.

[1-4] In the compound of formula (I), D is [1-4-a] a hydrogen atom, a group -CO-R<sub>5</sub> (wherein R<sub>5</sub> is hydrogen atom or a substituent), or an optionally substituted C<sub>1-6</sub> alkyl group (preferably a C<sub>1-6</sub> alkyl group optionally substituted with R<sub>15</sub> as described below).

**[0060]** R<sub>5</sub> is preferably a hydrogen atom; a hydroxyl group; a C<sub>1-6</sub> alkyl group; a C<sub>1-6</sub> alkoxy group; a C<sub>1-6</sub> alkoxy-carbonylalkyl group; a phenoxy group or a benzyloxy group each of which is optionally substituted with a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a halogen atom; or an optionally substituted amino group, and in particular, a group -NR<sub>6</sub>R<sub>7</sub> (wherein

R<sub>6</sub> and R<sub>7</sub> are independently hydrogen atom, a C<sub>1-6</sub> alkyl, a C<sub>4-7</sub> cycloalkyl, or a C<sub>2-6</sub> alkenyl; or R<sub>6</sub> and R<sub>7</sub> may together form a five- to seven-membered heterocyclic ring with the nitrogen atom to which R<sub>6</sub> and R<sub>7</sub> are binding, the heterocyclic ring optionally further comprising 1 or 2 heteroatoms selected from N, S, and O; and such substituent R<sub>5</sub> is optionally further substituted with a group selected from hydroxyl, amino, carboxyl, C<sub>1-6</sub> alkoxycarbonyl, oxo, C<sub>1-6</sub> alkyl, hydroxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy-C<sub>1-6</sub> alkyl, carboxy C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl-C<sub>1-6</sub> alkoxycarbonyl, and carbamoyl C<sub>1-6</sub> alkoxy). [1-4-b] More preferably, D is a hydrogen atom; or

1) a group selected from a carboxyl group; a C<sub>1-6</sub> alkylcarbonyl group; a C<sub>1-6</sub> alkoxy carbonyl group; a C<sub>1-6</sub> alkoxy carbonylalkylcarbonyl group; a phenoxycarbonyl group optionally substituted with a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a halogen atom; a benzyloxycarbonyl group optionally substituted with a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a halogen atom;

2) a carbamoyl group which is optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl; a C<sub>1-6</sub> alkoxy carbamoyl group; a C<sub>1-6</sub> alkoxy carbonylalkylcarbamoyl group; a cyclic amino carbonyl group optionally substituted with oxo, hydroxyl, amino, or carboxyl (and in particular, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-ylcarbonyl, a piperazin-1-ylcarbonyl, a 4-morpholinocarbonyl, a thiomorpholinocarbonyl, or a 1,1-dioxo-4-thiomorpholinocarbonyl); a N-phenylcarbamoyl group; or a group selected from the groups represented by -CONH(CH<sub>2</sub>)<sub>p</sub>S(O)<sub>q</sub>R<sub>10</sub> and -CONH(CH<sub>2</sub>)<sub>t</sub>NR<sub>11</sub>R<sub>12</sub> (wherein R<sub>10</sub>, R<sub>11</sub> and R<sub>12</sub> are independently a hydrogen atom, a C<sub>1-6</sub> alkyl group, a phenyl group, or a C<sub>1-6</sub> alkylphenyl group; p is an integer of 0 to 4; q is an integer of 0 to 2; and t is an integer of 1 to 4); or

3) a C<sub>1-6</sub> alkyl group (preferably methyl or ethyl) optionally substituted with R<sub>15</sub> (wherein R<sub>15</sub> represents a carboxyl group; a C<sub>1-6</sub> alkoxy carbonyl group; hydroxyl group; a C<sub>1-6</sub> alkoxy group; a C<sub>1-6</sub> alkanoyloxy group; an amino group; a mono- or di-substituted C<sub>1-6</sub> alkylamino group; a C<sub>1-6</sub> alkanoylamino group; a C<sub>1-6</sub> alkylsulfonylamino group; a five- or six-membered cyclic amino group optionally substituted with oxo, hydroxyl, amino, or carboxyl (and in particular, a pyrrolidin-1-yl, a piperidin-1-yl, a piperazin-1-yl, a 4-morpholino, a thiomorpholino, or a 1,1-dioxo-4-thiomorpholino); or a N-hydroxyimino group (an aldoxime group)).

[1-4-c] Still more preferably, D is a hydrogen atom; or

1) a group selected from a carboxyl group, a C<sub>1-2</sub> alkylcarbonyl group, a C<sub>1-2</sub> alkoxy carbonyl group, and a C<sub>1-2</sub> alkoxy carbonyl alkylcarbonyl group; or a group selected from a phenoxycarbonyl group which is optionally substituted with a C<sub>1-2</sub> alkyl, a C<sub>1-2</sub> alkoxy, or a halogen atom, or a benzyloxy carbonyl group which is optionally substituted with a C<sub>1-2</sub> alkyl, a C<sub>1-2</sub> alkoxy, or a halogen atom;

2) a carbamoyl group which is optionally mono- or di-substituted with a C<sub>1-2</sub> alkyl; a C<sub>1-2</sub> alkoxy carbamoyl group; a C<sub>1-2</sub> alkoxy carbonyl alkyl carbamoyl group; a cyclic amino carbonyl group which is optionally substituted with oxo, hydroxyl, amino or carboxyl (and in particular, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-ylcarbonyl, a piperazin-1-ylcarbonyl, a 4-morpholino carbonyl group, a thiomorpholino carbonyl group, or a 1,1-dioxo-4-thiomorpholino carbonyl group); or

3) a methyl group or an ethyl group optionally substituted with R<sub>15'</sub> (wherein R<sub>15'</sub> represents a carboxyl group; a C<sub>1-2</sub> alkoxy carbonyl group; a hydroxyl group; a C<sub>1-2</sub> alkoxy group; a C<sub>1-3</sub> alkanoyloxy group; an amino group; a mono- or di-substituted C<sub>1-2</sub> alkylamino group; a C<sub>1-2</sub> alkanoylamino group; a pyrrolidin-1-yl group, a piperidin-1-yl group, a piperazin-1-yl group, a 4-morpholino group, a thiomorpholino group or a 1,1-dioxo-4-thiomorpholino group, each of which is optionally substituted with oxo, hydroxyl, amino or carboxyl).

[1-5] In formula (I), X is

[1-5-a] a methine group optionally substituted with A'-B'-(wherein A' is a group selected from those defined for A and B' is a group selected from those defined for B), or nitrogen atom, and

[1-5-b] preferably a methine group or a nitrogen atom, and [1-5-c] more preferably a nitrogen atom. [1-6] In formula (I), Y is

[1-6-a] an oxygen atom,  $-S(O)_y-$  (wherein  $y$  is an integer of 0 to 2), or an optionally substituted imino group ( $-NH-$ ) wherein the substituent for the imino group is 1)  $-CO-R_5$  (wherein  $R_5$  is a group selected from those as defined above); 2) a  $C_{1-6}$  alkyl group optionally substituted with  $R_{15}$  (wherein  $R_{15}$  is a group selected from those as defined above); 3) a  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy or phenyl group which is optionally substituted with a halogen atom; or 4) a N-oxide group, as described for D in [4].

[1-6-b] Preferably, Y is an oxygen atom, or

[1-6-c] alternatively,  $-S(O)_y-$  (wherein y is an integer of 0 to 2, and preferably 0), or

[1-6-d] an unsubstituted imino group (-NH-).

[1-7] In formula (I), Z is

[1-7-a] a methylene group, a carbonyl group, or a thiocarbonyl group, and

[1-7-b] preferably a carbonyl group,

[1-8] In formula (I), T is

[1-8-a] -S(O)<sub>z</sub>- (wherein z is an integer of 0 to 2, and preferably 2), carbonyl group, or an optionally substituted C<sub>1-2</sub>

alkylene group (in particular, C<sub>1-2</sub> alkylene group optionally substituted with an optionally halogenated C<sub>1-6</sub> alkyl group or an optionally halogenated C<sub>1-6</sub> alkoxy group), and

[1-8-b] preferably, -SO<sub>2</sub>- or -CH<sub>2</sub>-.

[1-9] In formula (I), l, m, and n are

[1-9-a] independently an integer selected from 0, 1 and 2 with the proviso that l and m are not simultaneously 0, and [1-9-b] more preferably, l is 1; m is 0 or 1; and n is 1. [1-10] In formula (I), r is 0 or 1. The bond indicated by the broken line and the solid line is a single bond or a double bond (when r is 0).

[1-11] Exemplary substituents of the ring containing X, the ring containing Y, and the ring containing Z include an oxo group (=O); a hydroxyimino group (=N~OH); an alkoxyimino groups (=N~ORi wherein Ri is a C<sub>1-6</sub> alkyl groups optionally substituted with a substituent which is preferably a group selected from halogen, hydroxyl, and carboxyl); and groups shown for D in [1-4], and the preferable substituents are an oxo group, a hydroxyl group, a carboxyl group, a halogen atoms, a C<sub>1-6</sub> alkyl groups, a C<sub>2-6</sub> alkenyl groups, and a C<sub>2-6</sub> alkynyl groups. Among these, the C<sub>1-6</sub> alkyl groups, the C<sub>2-6</sub> alkenyl groups, and the C<sub>2-6</sub> alkynyl group are optionally further substituted with substituent RI (wherein RI represents a group selected from C<sub>1-6</sub> alkoxy; C<sub>1-6</sub> alkoxy carbonyl; carboxyl; carbamoyl optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; halogen; C<sub>1-6</sub> alkyl; halogenated C<sub>1-6</sub> alkyl; amino optionally mono- or di-substituted with a C<sub>1-6</sub> alkyl; C<sub>2-6</sub> alkenyl amino; nitro; hydroxyl; oxo; cyano; and amidino). Particularly preferable substituents are an oxo group, a C<sub>1-6</sub> alkoxy groups, and a carboxyl group.

[0061] Preferably,

[1-11-a] the substituent of the ring containing X is preferably an oxo group, a hydroxyl group, a lower alkyl group, or a lower alkoxyalkyl group;

[1-11-b] the substituent of the ring containing Y is preferably an oxo group, a hydroxyimino group, or a substituted alkoxyimino group (=N~ORi wherein Ri is a C<sub>1-6</sub> alkyl group optionally substituted with a substituent which is preferably selected from halogen,

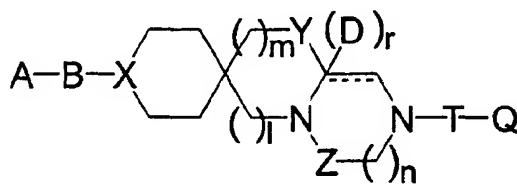
hydroxyl, and carboxy); and

[1-11-c] the substituent of the ring containing Z is preferably an oxo group, a hydroxyimino group, or a substituted alkoxyimino group (=N~ORi wherein Ri is a C<sub>1-6</sub> alkyl group optionally substituted with a substituent which is preferably selected from halogen, hydroxyl, and carboxy), and the position of the substitution includes replacement of the carbonyl defined as Z with the hydroxyimino group or the substituted alkoxyimino group.

[0062] With regard to the compounds of formula (I), the preferable compounds may be defined by arbitrary combinations of the [1-1] to [1-11] as described above. Examples of the compounds of such combination are shown below in [1-12].

[1-12]

[0063] In formula (I),



formula (I)

[0064] Q is (1) a C<sub>1-10</sub> alkyl group; (2) a C<sub>2-6</sub> alkenyl group; (3) a C<sub>2-6</sub> alkynyl group; (4) a C<sub>3-9</sub> cycloalkyl group; (5) a C<sub>3-6</sub> cycloalkenyl group; (6) a C<sub>4-6</sub> cycloalkadienyl group; (7) a C<sub>6-14</sub> aryl group; or (8) a heterocyclic group containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom in addition to the carbon atoms which is (i) a five- or six-membered, monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered, fused aromatic heterocyclic group, or (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group; and each group of the above (1) to (8) is either unsubstituted or substituted at 1 to 5 arbitrary positions with a substituent of the class selected from (a) to (g) as described below:

(a) C<sub>1-6</sub> alkyl groups and C<sub>6-14</sub> aryl groups which are optionally further substituted with substituent RI (wherein RI represents a C<sub>1-6</sub> alkoxy group, a halogen, a C<sub>1-6</sub> alkyl group, an amino group, a hydroxyl group, a cyano group or an amidino group);

(b) a heterocyclic group containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom



in addition to the carbon atoms which is (i) a five- or six-membered, monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered, fused aromatic heterocyclic group, or (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic groups; wherein the heterocyclic groups are optionally further substituted with a substituent RII (wherein RII represents a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, or a benzoyl group);

(c) an amino group optionally substituted with a substituent selected from substituents RIII (wherein RIII represents a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, a benzoyl group, or an optionally halogenated C<sub>1-6</sub> alkoxy-carbonyl group, a C<sub>1-6</sub> alkyl imido group, a formimido group, or an amidino group);

(d) an imido group, an amidino group, a hydroxyl group and a thiol group which are optionally further substituted with a group selected from C<sub>1-6</sub> alkyl groups, C<sub>1-6</sub> alkanoyl groups, a benzoyl group and optionally halogenated C<sub>1-6</sub> alkoxy-carbonyl groups;

(e) a halogen atom, a cyano group and a nitro group;

(f) a carboxyl group, a C<sub>1-6</sub> alkoxy-carbonyl groups, a C<sub>7-12</sub> aryloxy-carbonyl groups, and a C<sub>6-10</sub> aryl-C<sub>1-4</sub> alkoxy-carbonyl group wherein the aryl group in such substituents is optionally further substituted with substituent RIV (wherein RIV represents hydroxyl, amino group optionally mono- or di-substituted with a group selected from substituents RIII of (c) as described above, a halogen atom, a nitro group, a cyano group, a C<sub>1-6</sub> alkyl group which is optionally substituted with 1 to 5 halogen atoms, or an alkoxy group which is optionally substituted with 1 to 5 halogen atoms); and

(g) -CO-RV wherein RV represents a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-10</sub> aralkyl group, or a heterocyclic group, and the heterocyclic group is the one containing 1 to 4 heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom in addition to the carbon atoms which is (i) a five- or six-membered, monocyclic aromatic heterocyclic group, (ii) an eight- to twelve-membered, fused aromatic heterocyclic group, or (iii) a three- to eight-membered, saturated or unsaturated, non-aromatic heterocyclic group;

**[0065]** T is -S(O)<sub>z</sub>- (wherein z is an integer of 0 to 2, and preferably 2), a carbonyl group, or an optionally substituted C<sub>1-2</sub> alkylene group (and in particular, a C<sub>1-2</sub> alkylene group which is optionally substituted with an optionally halogenated C<sub>1-6</sub> alkyl group or an optionally halogenated C<sub>1-6</sub> alkoxy group); and preferably -SO<sub>2</sub>- or -CH<sub>2</sub>-;

A is a hydrogen atom, or

(1) a five- or six-membered, aromatic or non-aromatic, monocyclic heterocyclic group which may contain 1 to 4 nitrogen atoms or 1 to 3 oxygen atoms or sulfur atoms in addition to the carbon atoms; wherein the ring is optionally further substituted with the substituent of (a) to (d), below:

(a) a halogen atom; (b) an amino group; (c) a C<sub>1-6</sub> alkyl group optionally substituted with a substituent selected from halogen, amino, carboxyl and hydroxy; and (d) a carboxyl group, a C<sub>1-6</sub> alkoxy-carbonyl group, a C<sub>7-12</sub> aryloxy-carbonyl group, and a C<sub>1-6</sub> aryl-C<sub>1-4</sub> alkoxy-carbonyl group, wherein the aryl is optionally substituted with substituent RIV (wherein RIV represents hydroxyl; an amino group optionally mono- or di-substituted with substituent RII (a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl, and benzoyl); a halogen atom; a nitro group; a cyano group; a C<sub>1-6</sub> alkyl group optionally substituted with 1 to 5 halogen atoms; or an alkoxy group which is optionally substituted with 1 to 5 halogen atoms);

(2) an amino group optionally mono- or di-substituted with a C<sub>1-10</sub> alkyl group or a C<sub>6-14</sub> aryl group; or

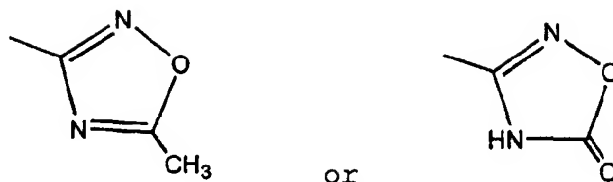
(3) a group: -N(Ra'')-C(Ra')=N-Ra or a group:

-C(Ra')=N-Ra wherein

Ra'' is a hydrogen atom or a C<sub>1-6</sub> alkyl group;

Ra' is a hydrogen atom, a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, a benzoyl group, an amino group mono- or di-substituted with a group selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkanoyl and benzoyl, or a C<sub>1-6</sub> alkoxy group; and

Ra is a hydrogen atom, a C<sub>1-6</sub> alkyl group, a C<sub>1-6</sub> alkanoyl group, or a benzoyl group; or alternatively the -C(Ra')=N-Ra moiety in each group may form



B is a single bond,  $-\text{SO}_2-$ , or an optionally substituted  $\text{C}_{1-2}$  alkylene;

D is a hydrogen atom; a group  $-\text{CO}-\text{R}_5$  (wherein  $\text{R}_5$  is hydrogen atom or a substituent); or an optionally substituted  $\text{C}_{1-6}$  alkyl group (and preferably a  $\text{C}_{1-6}$  alkyl group optionally substituted with  $\text{R}_{15}$  as described below); wherein

$\text{R}_5$  is preferably a hydrogen atom, hydroxyl, a  $\text{C}_{1-6}$  alkyl, a  $\text{C}_{1-6}$  alkoxy, a  $\text{C}_{1-6}$  alkoxyalkyl, or an optionally substituted amino group, and in particular, group  $-\text{NR}_6\text{R}_7$  (wherein  $\text{R}_6$  and  $\text{R}_7$  are independently hydrogen atom, a  $\text{C}_{1-6}$  alkyl, a  $\text{C}_{4-7}$  cycloalkyl, or a  $\text{C}_{2-6}$  alkenyl; or  $\text{R}_6$  and  $\text{R}_7$  may together form a five- to seven-membered heterocyclic ring with the nitrogen atom to which  $\text{R}_6$  and  $\text{R}_7$  are binding, the heterocyclic ring optionally further comprising 1 or 2 heteroatoms selected from N, S, and O); wherein the substituent  $\text{R}_5$  is optionally further substituted with a group selected from hydroxyl, amino, carboxyl,  $\text{C}_{1-6}$  alkoxyalkyl, oxo,  $\text{C}_{1-6}$  alkyl, hydroxy- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy- $\text{C}_{1-6}$  alkyl, carboxy- $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkyl- $\text{C}_{1-6}$  alkoxyalkyl, and carbamoyl- $\text{C}_{1-6}$  alkoxy; and

D is more preferably a hydrogen atom; or

1) a group selected from carboxyl group,  $\text{C}_{1-6}$  alkylcarbonyl groups,  $\text{C}_{1-6}$  alkoxyalkyl groups, and  $\text{C}_{1-6}$  alkoxyalkylalkylcarbonyl groups;

2) a carbamoyl group mono- or di-substituted with a  $\text{C}_{1-6}$  alkyl; a  $\text{C}_{1-6}$  alkoxyalkyl group; a  $\text{C}_{1-6}$  alkoxyalkylalkylcarbonyl group; a cyclic amino carbonyl group optionally substituted with oxo, hydroxyl, amino, or carboxyl (and in particular, pyrrolidin-1-ylcarbonyl group, piperidin-1-ylcarbonyl, piperazin-1-ylcarbonyl, 4-morpholinocarbonyl, thiomorpholinocarbonyl, or 1,1-dioxo-4-thiomorpholinocarbonyl); N-phenylcarbamoyl group; or a group selected from the groups represented by  $-\text{CONH}(\text{CH}_2)_p\text{S}(\text{O})_q\text{R}_{10}$  and  $-\text{CONH}(\text{CH}_2)_t\text{NR}_{11}\text{R}_{12}$  (wherein  $\text{R}_{10}$ ,  $\text{R}_{11}$  and  $\text{R}_{12}$  are independently hydrogen atom, a  $\text{C}_{1-6}$  alkyl group, phenyl group, or a  $\text{C}_{1-6}$  alkylphenyl group; p is an integer of 0 to 4; q is an integer of 0 to 2; and t is an integer of 1 to 4); or

3) a  $\text{C}_{1-6}$  alkyl group (preferably methyl or ethyl) optionally substituted with  $\text{R}_{15}$  (wherein  $\text{R}_{15}$  represents a carboxyl group; a  $\text{C}_{1-6}$  alkoxyalkyl group; a hydroxyl group; a  $\text{C}_{1-6}$  alkoxy group; a  $\text{C}_{1-6}$  alkanoyloxy group; an amino group; a mono- or di-substituted  $\text{C}_{1-6}$  alkylamino group; a  $\text{C}_{1-6}$  alkanoylamino group; a  $\text{C}_{1-6}$  alkylsulfonylamino group; a five- or six-membered cyclic amino group which is optionally substituted with oxo, hydroxyl, amino or carboxyl (and in particular, a pyrrolidin-1-yl, a piperidin-1-yl, a piperazin-1-yl, a 4-morpholino, a thiomorpholino, or a 1,1-dioxo-4-thiomorpholino); a N-hydroxyimino group (an aldoxime group));

X is CH or N;

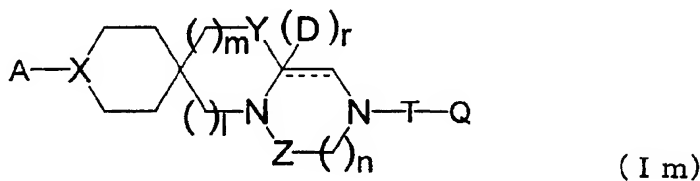
Y is oxygen atom,  $-\text{S}(\text{O})_y-$  (wherein y is an integer of 0 to 2, and preferably 0), or NH;

Z is a methylene group, a carbonyl group, or a thiocarbonyl group (and preferably a carbonyl group); and

l, m, and n are independently an integer selected from 0, 1 and 2 with the proviso that l and m are not simultaneously 0; and r is an integer of 0 or 1, and the bond indicated by the broken line and the solid line is a single bond or a double bond (when r is 0).

[1-13]

**[0066]** A more preferable compound within the range as described above is the compound represented by formula (Im):

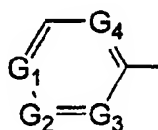


**[0067]** In formula (Im), X, Y, Z, D, Q, l, m, n, and r are as defined for [1-12]; T is  $-\text{SO}_2-$  or  $-\text{CH}_2-$ ; and A is a five-

membered aromatic monocyclic heterocyclic group which may contain 1 to 4 nitrogen atoms or 1 to 3 oxygen atoms or sulfur atoms in addition to the carbon atoms (and in particular,



or the group:



wherein  $G_1$ ,  $G_2$ ,  $G_3$ , and  $G_4$  are independently CH or N, and preferably, at least one of the  $G_1$ ,  $G_2$ ,  $G_3$ , and  $G_4$  is N. The more preferred are those wherein  $G_1$  is N, and  $G_2$ ,  $G_3$ , and  $G_4$  are CH;  $G_2$  is N, and  $G_1$ ,  $G_3$ , and  $G_4$  are CH;  $G_3$  is N, and  $G_1$ ,  $G_2$ , and  $G_4$  are CH;  $G_1$  and  $G_2$  are N, and  $G_3$  and  $G_4$  are CH;  $G_1$  and  $G_3$  are N, and  $G_2$  and  $G_4$  are CH;  $G_1$ ,  $G_2$ , and  $G_4$  are N, and  $G_3$  is CH; and  $G_1$ ,  $G_3$ , and  $G_4$  are N, and  $G_2$  is CH; and the still more preferred are those wherein  $G_1$  is N, and  $G_2$ ,  $G_3$ , and  $G_4$  are CH;  $G_1$  and  $G_3$  are N, and  $G_2$  and  $G_4$  are CH; and  $G_1$ ,  $G_3$  and  $G_4$  are N, and  $G_2$  is CH.

**[0068]** Exemplary groups are 4-pyridyl, 3-pyridyl, 2-pyridyl, 4-pyrimidinyl, 3-pyrimidinyl, and 4-pyridazinyl, and the preferred are 4-pyridyl and 4-pyrimidinyl.

**[0069]** It should be noted that, although N-oxide can be formed by the N at any of the  $G_1$  to  $G_4$ , N-oxide at  $G_1$  is preferable (and in particular, the one wherein at least  $G_1$  is N is preferable). In addition, all of the five- or six-membered rings are optionally mono- or di-substituted by any of the substituents (a) to (d) as described for A.

**[0070]** Among these, A is preferably unsubstituted 4-pyridyl group or 4-pyridyl group mono-substituted with a halogen atom, amino group, methyl group, ethyl group, hydroxyl group, or hydroxymethyl group; and most preferably unsubstituted 4-pyridyl group.

**[0071]** Exemplary preferable compounds are:

- 40 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 45 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl) spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 50 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 55 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfone;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 5 (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(isopropoxycarbonyl)-7-oxa-1'-(4-pyridyl) spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(propoxycarbonyl)-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 (-)-6-(allyloxycarbonyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 10 (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 (-)-1,4-diaza-6-(t-butoxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 15 ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;  
 (+)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;  
 (-)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;  
 20 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-2-oxospiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-1'-yl]pyridine 1-oxide;  
 1'-acetimidoyl-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 25 6-(aminomethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylaminomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(morpholinomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 30 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;  
 ammonium 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-6-yl]butylate;  
 35 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(7-chloro-2H-benzopyran-3-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 40 1,4-diaza-4-(7-chloro-2H-benzopyran-3-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chlorobenzothiophen-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 45 1,4-diaza-4-(6-chlorobenzothiophen-2-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(5-chlorobenzofuran-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 50 1,4-diaza-4-(5-chlorobenzofuran-2-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(6-chlorobenzofuran-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one; and  
 (+) or (-) optical isomers of such compounds, and their pharmaceutically acceptable salts (for example, methanesulfonate (mono-salt or di-salt)).

[2] Second aspect of the present invention is a pharmaceutical composition characterized by its inclusion of the compound represented by formula (I) or its pharmaceutically acceptable salt as an effective component. [2-a] More specifically, the pharmaceutical composition is

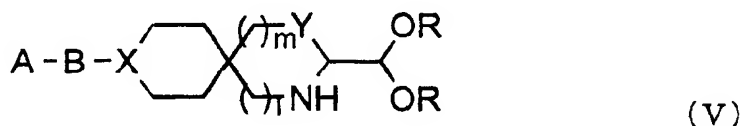
- 1) an anticoagulant; or a prophylactic and/or therapeutic agent for diseases induced by thrombosis or embolism;  
 2) a prophylactic and/or therapeutic agent for diseases wherein an anticoagulant is effective; or a prophylactic and/or therapeutic agent for diseases wherein inhibition of FXa is effective;  
 3) a prophylactic agent for embolism associated with atrial fibrillation/artificial valve or valvular heart disease (and preferably, a prophylactic agent for onset of cerebral embolism associated with these diseases); or a prophylactic and/or therapeutic agent for (and in particular, a prophylactic agent for recurrence of) transient ischemic attack; or  
 4) a prophylactic and/or therapeutic agent for DIC; a prophylactic and/or therapeutic agent for influenza virus infection; or a prophylactic and/or therapeutic agent for deep vein thrombosis.

[3] Third aspect of the present invention is a FXa inhibitor characterized by its inclusion of the compound represented by formula (I) or its pharmaceutically acceptable salt.

[3-a] More specifically, the FXa inhibitor is an inhibitor specific for FXa characterized by its inclusion of the compound represented by formula (I) or its pharmaceutically acceptable salt as an effective component; a FXa inhibitor which can be orally administered; and an inhibitor specific for FXa which can be orally administered.

[3-b] The FXa inhibitor is a reagent characterized by its use of the compound represented by formula (I) or its pharmaceutically acceptable salt. Exemplary such reagents include a reagent for diagnosing abnormality of blood coagulation in a mammal wherein the FXa inhibitory action is utilized; a reagent for use in physiological experiments wherein quantitative FXa inhibitory action is utilized.

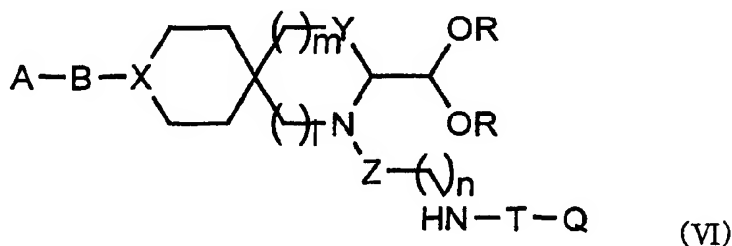
[4] Fourth aspect of the present invention is the compound represented by formula (V):



(wherein A, B, X, Y, l, and m and the preferred embodiments are as defined above for the formula (I); the ring containing X and the ring containing Y are independently optionally substituted; R is hydrogen atom, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, or a C<sub>1-6</sub> alkyl group optionally substituted with hydroxyl or a halogen atom, or the two R may together represent a C<sub>2-4</sub> alkylene group which is optionally substituted with C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, hydroxyl, or a halogen atom.)

**[0072]** The compound of formula (V) is a novel compound useful as an intermediate in the synthesis of the compound of formula (I). It should be noted that the preferable range for A, B, X, Y, l, and m are as described above for the preferable embodiments of the formula (I). R is preferably methyl group, ethyl group, 1,2-ethylene group, or 1,3-propylene group.

[5] Fifth aspect of the present invention is the compound of formula (VI):

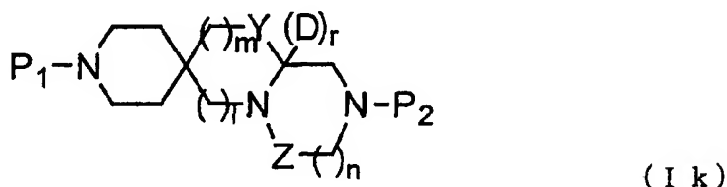


(wherein A, B, X, Y, Z, T, Q, l, m, and n and the preferred embodiments are as defined above for the formula (I); the ring containing X and the ring containing Y are independently optionally substituted; the alkylene group which binds to Z when n is 1 or more is optionally substituted; R is hydrogen atom, a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a C<sub>1-6</sub> alkyl group optionally substituted with hydroxyl or a halogen atom, or the two R may together represent a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, a C<sub>2-4</sub> alkylene group optionally substituted with hydroxyl or a halogen atom.)

**[0073]** The compound of formula (VI) is also a novel compound useful as an intermediate in the synthesis of the compound of formula (I). It should be noted that the preferable range for A, B, X, Y, l, and m are as described above

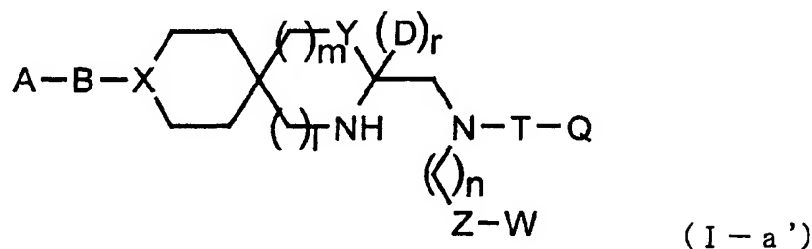
for the preferable embodiments of the formula (I). R is preferably methyl group, ethyl group, 1,2-ethylene group, or 1,3-propylene group.

[6] Sixth aspect of the present invention is the compound of formula (Ik):



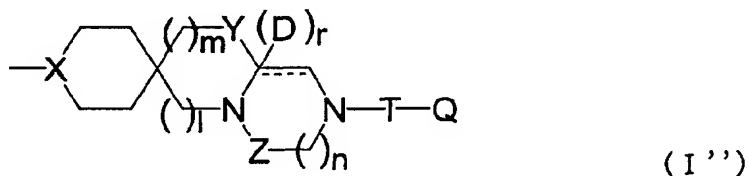
(wherein  $P_1$  and  $P_2$  are independently hydrogen atom or a protective group for the imino group; Y, Z, D, I, m, n, and r and the preferred embodiments are as defined above for the formula (I); and the three rings are independently optionally substituted). Exemplary imino protective groups are aralkyl groups such as benzyl group; acyl groups such as acetyl group; alkoxycarbonyl groups such as benzyloxycarbonyl and t-butoxycarbonyl; as well as the imino protective groups described in comprehensive volumes such as Protective Groups in Organic Synthesis, Second edition, 1991, John Wiley & Sons, Inc.

[7] Seventh aspect of the present invention is the compound of formula (I-a'):



(wherein A, B, D, X, Y, Z, Q, T, I, m, n, and r and the preferred embodiments are as defined above for the formula (I); W is a leaving group or a group convertible into a leaving group; the ring containing X and the ring containing Y are independently optionally substituted; and the alkylene group which binds to Z when n is 1 or more is optionally substituted). Exemplary leaving groups are halogen atoms; acyloxy groups such as acetyloxy; and substituted sulfonyloxy groups such as methanesulfonyloxy and p-toluenesulfonyloxy groups, and if necessary, a general textbook on organic chemistry may be referred for other examples.

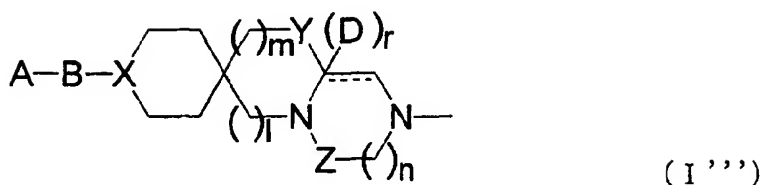
[8] Eighth aspect of the present invention is a compound exhibiting FXa inhibitory activity which has a partial structure represented by formula (I'') in its molecule, and the salt thereof.



(In the formula,  $-X=$  is  $-CH=$  or  $-N=$ ; the three rings, namely, the ring containing X, the ring containing Y, and the ring containing Z are independently optionally substituted; and Y, Z, D, T, Q, I, m, n, and r and the preferred embodiments are as defined above for the formula (I)).

**[0074]** The partial structure represented by formula (I'') is a novel partial structure which plays an important role when the compound develops its FXa inhibitory activity.

[9] Ninth aspect of the present invention is a compound exhibiting FXa inhibitory activity which has a partial structure represented by formula (I''') in its molecule, and the salt thereof.

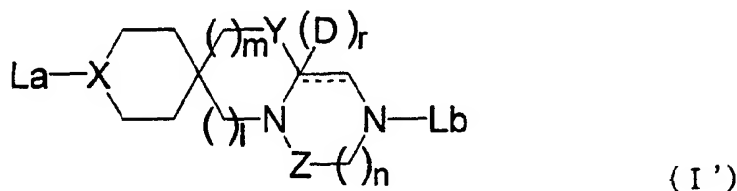


10 (In the formula, X is methine group or nitrogen atom; the three rings, namely, the ring containing X, the ring containing Y, and the ring containing Z are independently optionally substituted; and A, B, Y, Z, D, I, m, n, and r and the preferred embodiments are as defined above for the formula (I)).

15 [0075] The partial structure represented by formula (I'') is a novel partial structure which plays an important role when the compound develops its FXa inhibitory activity.

[10] Tenth aspect of the present invention is

[10-a] a compound having FXa inhibitory activity represented by the formula (I') or its pharmaceutically acceptable salt:



wherein

30 D is hydrogen atom, -CO-R<sub>5</sub> (wherein R<sub>5</sub> is hydrogen atom or a substituent), or an optionally substituted C<sub>1-6</sub> alkyl group,

X is a methine group or a nitrogen atom;

35 Y is an oxygen atom, -S(O)<sub>y</sub>-, or an optionally substituted imino group (-NH-);

the ring containing Y may optionally have an oxo group as a substituent;

Z is a methylene group, a carbonyl group, or a thiocarbonyl group;

I, m, n, and y are independently an integer selected from 0, 1 and 2, with the proviso that I and m are not simultaneously 0, and r is an integer of 0 or 1;

40 the bond indicated by the broken line and the solid line represents a single bond or a double bond (when r is 0); and

La and Lb are groups involved in the binding of the compound of the formula (I') to the FXa, wherein

La represents a group having a basic moiety which associates with S3 pocket of FXa [a space formed at least by amino residues Trp215, Phe174, Tyr99, Thr98, Glu97, and Lys96], and

45 Lb represents a group having a hydrophobic moiety which binds to S1 pocket of FXa [a space formed at least by amino acid residues Val213, Ser214, Trp215, Gly216, Glu217, Gly218, Cys220, Asp189, Ala190, Cys191, Gln192, Gly193, Asp194, Ser195, Gly226, Ile227, and Tyr228], and which interacts with the Tyr228 side chain in the S1 pocket but which does not form a covalent bond with Ser195 in the active center. (The amino acid No. of the FXa is indicated by chymotrypsin No. used in Protein Data Bank (PDB), Registration ID: 1FAX (J. Biol. Chem. 1996 Nov. 22; 271(47): 29988-92)).

50 [0076] The amino acid No. of the FXa corresponding to the chymotrypsin No. is shown in FIG. 42 in the form of a table. [10-b] Preferably, the compound of formula (I') is the one wherein, when the compound of formula (I') binds to the FXa, the interaction of the Lb with the Tyr228 is an interaction mediated by the halogen atom, methyl group, ethyl group, or methoxy group (preferably chlorine atom or bromine atom) constituting a part of the hydrophobic moiety of the Lb. A preferable example of Lb is a group represented by the combination of Q in [1-1-d] and T in [1-8-a].

55 [10-c] More preferably, the compound of formula (I') is the one wherein, when the hydrophobic moiety of the Lb interacts with the Tyr228 in the binding of the compound of formula (I') to the FXa, the distance between the centroid (the coordinate obtained by calculating the average for each of X, Y, and Z coordinates of all heavy atoms included in the partial structure; hereinafter simply referred to as centroid) of the hydrophobic moiety of the Lb and the centroid of the

Tyr228 side chain is within the range of 6.9 to 7.9 Å.

[10-d] The compound is also a FXa inhibitory compound which further satisfies at least one of the following conditions 1) to 3) in addition to the [10-a] to [10-c] as described above.

1) When the compound binds to the FXa, the hydrophobic moiety of the Lb does not either partly or entirely undergo an electrostatic interaction with the Asp189 of the S1 pocket.

2) When the compound binds to the FXa, position of the centroid of the hydrophobic moiety of the Lb satisfies in the S1 pocket at least two of the following conditions that such position is:

- i) at a distance of 3.6 to 4.6 Å from the Cys191 backbone C<sub>α</sub> atom;
- ii) at a distance of 6.2 to 7.2 Å from the Ser195 backbone C<sub>α</sub> atom;
- iii) at a distance of 5.5 to 6.5 Å from the Ser214 backbone C<sub>α</sub> atom;
- iv) at a distance of 3.6 to 4.6 Å from the Trp215 backbone C<sub>α</sub> atom;
- v) at a distance of 6.7 to 7.7 Å from the Glu217 backbone C<sub>α</sub> atom; and
- vi) at a distance of 5.8 to 6.8 Å from the Cys220 backbone C<sub>α</sub> atom.

3) When the compound binds to the FXa, position of the centroid of the partial structure including the basic moiety of the La satisfies in the S3 pocket at least two of the following conditions that such position is:

- i) at a distance of 4.1 to 5.5 Å from the Tyr99 side chain centroid;
- ii) at a distance of 3.1 to 4.5 Å from the Phe174 side chain centroid;
- iii) at a distance of 4.1 to 5.5 Å from the Trp215 side chain centroid;
- iv) at a distance of 4.1 to 6.3 Å from the Lys96 backbone carbonyl oxygen atom; and
- v) at a distance of 3.5 to 5.1 Å from the Glu97 backbone carbonyl oxygen atom.

4) La has an optionally substituted, five- to six-membered, aromatic monocyclic heterocyclic group.

[11] Eleventh aspect of the present invention is a compound exhibiting FXa inhibitory activity which fulfills the binding conditions of any one of embodiments [10-a] to [10-d] when the compound has formed a complex with the FXa and the complex is in its crystalline state; and preferably, the compound is the one which satisfies the binding condition of [10-d].

[12] Twelfth aspect of the present invention is a compound which satisfies all of the following conditions:

(1) the compound has a group including a basic moiety which associates with the S3 pocket of the Fxa [a space formed at least by amino residues Trp215, Phe174, Tyr99, Thr98, Glu97, and Lys96] when the complex of the compound with the FXa is in its crystalline state;

(2) the compound has a hydrophobic moiety which binds to the S1 pocket of FXa [a space formed at least by amino acid residues Val213, Ser214, Trp215, Gly216, Glu217, Gly218, Cys220, Asp189, Ala190, Cys191, Gln192, Gly193, Asp194, Ser195, Gly226, Ile227, and Tyr228] when the complex of the compound with the FXa is in its crystalline state;

(3) said hydrophobic moiety interacts with the Tyr228 side chain in the S1 pocket, but does not covalently bond to the Ser195 in the active center when the complex of the compound with the FXa is in its crystalline state; and

(4) the compound has FXa inhibitory activity.

[13] Thirteenth aspect of the present invention is a composition characterized by its inclusion of at least one compound according to eighth to twelfth aspect of the invention or its salt as an effective component. Such composition has FXa inhibitory activity, and therefore, the composition is on one hand useful as a prophylactic or therapeutic agent for the diseases described in the second aspect, and on the other hand as a FXa inhibitor described in the third aspect.

[14] Fourteenth aspect of the present invention is a pharmaceutical composition characterized by its inclusion of at least one compound according to eighth to twelfth aspect of the invention as an effective component.

[15] Fifteenth aspect of the present invention is a method for inhibiting FXa characterized in that the method comprises administration of the pharmaceutical composition according to the fourteenth aspect of the invention to a mammal requiring the FXa inhibition. The method is preferably the one characterized by that the administration is accomplished by oral administration.

[16] Sixteenth aspect of the present invention is a crystal of the complex of at least one compound according to eighth to twelfth aspect of the invention or its salt with FXa.

**[0077]** It should be noted that, with regard to the FXa inhibitory activity mentioned in the [10] to [16], IC<sub>50</sub> of up to 1 μM, preferably up to 0.5 μM, more preferably up to 0.1 μM, and most preferably up to 0.01 μM in a bioassay for FXa



can be added as a preferable option.

[17] Seventeenth aspect of the present invention is:

[17-a] a pharmacophore which is useful in identifying or designing an inhibitor which competitively binds to active site of the FXa or its fragment, and which satisfies all of the (a) to (c):

(a) it is the three-dimensional structural parameter which defines the binding mode when the inhibitor binds to S1 pocket of the FXa by its hydrophobic moiety, and which induces the interaction with the Tyr228 side chain in the S1 pocket;

(b) it is the three-dimensional structural parameter defining the binding mode when the inhibitor binds to S3 pocket of FXa by its basic moiety; and

(c) the inhibitor does not covalently bond to Ser195 in the active center.

**[0078]** It should be noted that amino acid No. of the FXa is indicated by chymotrypsin No. used in Protein Data Bank (PDB), Registration ID: 1FAX (J. Biol. Chem. 1996 Nov. 22; 271 (47): 29988-92).

**[0079]** The structure of the part of the compound which binds to the S1 pocket defined by the pharmacophore of the present invention is clearly different from the structure of the part reported for the prior art DX-9065a and the like in that the interaction with the Tyr228 is necessary, and that the electrostatic interaction with the Asp189 is not the prerequisite.

[17-b] a pharmacophore of [17-a] wherein

[17-b1] the interaction with the Tyr228 is an interaction mediated by the halogen atom, methyl group, ethyl group, or methoxy group (preferably chlorine atom or bromine atom) constituting a part of the hydrophobic moiety;

[17-b2] in the interaction with Tyr228, the distance between the centroid of the hydrophobic moiety and the centroid of the Tyr228 side chain is within the range of 6.9 to 7.9 Å;

[17-b3] the pharmacophore satisfies at least one of the following conditions 1) to 3):

1) when the compound binds to the FXa, the hydrophobic moiety does not either partly or entirely undergo an electrostatic interaction with the Asp189 of the S1 pocket;

2) when the compound binds to the FXa, position of the centroid of the hydrophobic moiety satisfies in the S1 pocket at least two of the following conditions that such position is:

- i) at a distance of 3.6 to 4.6 Å from the Cys191 backbone C<sub>α</sub> atom;
- ii) at a distance of 6.2 to 7.2 Å from the Ser195 backbone C<sub>α</sub> atom;
- iii) at a distance of 5.5 to 6.5 Å from the Ser214 backbone C<sub>α</sub> atom;
- iv) at a distance of 3.6 to 4.6 Å from the Trp215 backbone C<sub>α</sub> atom;
- v) at a distance of 6.7 to 7.7 Å from the Glu217 backbone C<sub>α</sub> atom; and
- vi) at a distance of 5.8 to 6.8 Å from the Cys220 backbone C<sub>α</sub> atom; and

3) when the compound binds to the FXa, centroid position of the partial structure including the basic moiety of the La satisfies in the S3 pocket at least two of the following conditions that such position is:

- i) at a distance of 4.1 to 5.5 Å from the Tyr99 side chain centroid;
- ii) at a distance of 3.1 to 4.5 Å from the Phe174 side chain centroid;
- iii) at a distance of 4.1 to 5.5 Å from the Trp215 side chain centroid;
- iv) at a distance of 4.1 to 6.3 Å from the Lys96 backbone carbonyl oxygen atom; and
- v) at a distance of 3.5 to 5.1 Å from the Glu97 backbone carbonyl oxygen atom; or

[17-b4] the pharmacophore satisfies all of the conditions 1) to 3) in [17-b3].

[18] Eighteenth aspect of the present invention is

[18-a] a method for identifying or designing an inhibitor which competitively binds to an active site of FXa or its fragment, wherein the inhibitor is screened by providing three-dimensional structural information of the active site to a computer system; identifying a compound which is assumed to bind to the FXa in a manner satisfying all of the conditions that:

(a) the compound associates with S1 pocket by its hydrophobic moiety and the moiety interacts with Tyr228,

(b) the compound associates with the inside of S3 pocket of the active site by its basic moiety, and

(c) the compound does not bind covalently with Ser195; and subjecting the compound to a biological assay which is capable of measuring FXa inhibitory activity to thereby determine whether the compound exhibits FXa inhibitory activity in the assay; and

[18-b] preferably, an inhibitor identification method within the scope of the aspect [18-a] characterized in that the method comprises: providing a computer system with the three-dimensional structural information of the FXa molecule containing the active site defined by coordinates of Table A (FIGS. 33 to 36) as described below; depicting the three-dimensional structure of the active site in the computer system; overlaying the three-dimensional structure of a test compound on the three-dimensional structure of the active site such that the three-dimensional structure of the test compound is arranged to meet all of the following conditions that:

- (a) the hydrophobic moiety is arranged in the S1 pocket so that the hydrophobic moiety can interact with the Tyr228;
- (b) the basic moiety is arranged in the S3 pocket; and
- (c) the compound does not bind covalently with the Ser195; evaluating whether the three-dimensional structure of the test compound spatially fits with the active site; preparing a test compound which spatially fits with the active site; and subjecting the test compound to a biological assay which is capable of measuring FXa inhibitory activity to thereby determine whether the test compound exhibits FXa inhibitory activity in the assay; or [18-c] alternatively, a drug designing method characterized in that an evaluation is conducted on a computer by using the three-dimensional structural information of the FXa or its fragment for a compound which satisfies the following association conditions:

- (a) the compound associates with the S1 pocket by its hydrophobic moiety, and the moiety interacts with the Tyr228;
- (b) the compound associates with the inside of the S3 pocket by its basic moiety; and
- (c) the compound does not bind covalently with Ser195; or

[18-d] a method within the scope of the aspects [18-a] to [18-c] which is:

[18-d1] a method for conducting identification or molecular design on the bases of the condition that interaction with the Tyr228 is mediated by the halogen atom, methyl group, ethyl group, or methoxy group (preferably chlorine atom or bromine atom) constituting a part of the hydrophobic moiety; or

[18-d2] a method for conducting identification or molecular design on the bases of the condition that, in the interaction with the Tyr228, the distance between the centroid of the hydrophobic moiety and the centroid of the Tyr228 side chain is within the range of 6.9 to 7.9 Å; or

[18-d3] a method for conducting identification or molecular design of a FXa inhibitory compound which satisfies at least one of the following conditions 1) to 3):

- 1) when the compound binds to the FXa, the hydrophobic moiety does not either partly or entirely undergo an electrostatic interaction with the Asp189 of the S1 pocket;
- 2) when the compound binds to the FXa, centroid position of the hydrophobic moiety satisfies in the S1 pocket at least two of the following conditions that such position is:

- i) at a distance of 3.6 to 4.6 Å from the Cys191 backbone C<sub>α</sub> atom;
- ii) at a distance of 6.2 to 7.2 Å from the Ser195 backbone C<sub>α</sub> atom;
- iii) at a distance of 5.5 to 6.5 Å from the Ser214 backbone C<sub>α</sub> atom;
- iv) at a distance of 3.6 to 4.6 Å from the Trp215 backbone C<sub>α</sub> atom;
- v) at a distance of 6.7 to 7.7 Å from the Glu217 backbone C<sub>α</sub> atom; and
- vi) at a distance of 5.8 to 6.8 Å from the Cys220 backbone C<sub>α</sub> atom; and

- 3) when the compound binds to the FXa, centroid position of the partial structure including the basic moiety of the La satisfies in the S3 pocket at least two of the following conditions that such position is:

- i) at a distance of 4.1 to 5.5 Å from the Tyr99 side chain centroid;
- ii) at a distance of 3.1 to 4.5 Å from the Phe174 side chain centroid;
- iii) at a distance of 4.1 to 5.5 Å from the Trp215 side chain centroid;
- iv) at a distance of 4.1 to 6.3 Å from the Lys96 backbone carbonyl oxygen atom; and
- v) at a distance of 3.5 to 5.1 Å from the Glu97 backbone carbonyl oxygen atom; or

[18-d4] a method for conducting the identification or the molecular design within the scope of the aspect [18-d3] on the condition that all of the conditions 1) to 3) are satisfied; or

[18-e] a method for conducting identification or molecular design of the inhibitor according to aspects [18-a] to [18-d], wherein, in providing a cross-linking group connecting the group binding to the S1 pocket and the group binding to the S3 pocket (for example La and Lb in formula (I')), a ring having spiro union is provided in the cross-linking group as a means for suppressing alteration of the conformation of the cross-linking group itself; or

[18-f] a compound identified or designed by, or a compound adapted for (a compound identifiable or designable by) the method for conducting identification or molecular design of the inhibitor according to aspects [18-a] to [18-e], which has FXa inhibitory activity in terms of  $IC_{50}$  determined by a bioassay of up to 1  $\mu M$ , and which was unknown at the time of the filing of the present invention; or

[18-g] a pharmaceutical composition containing as an effective component at least one compound identified or designed by, or a compound adapted for the method for conducting identification or molecular design of the inhibitor according to aspects [18-a] to [18-e], which has FXa inhibitory activity in terms of  $IC_{50}$  determined by a bioassay of up to 1  $\mu M$ , and (1) which was unknown at the time of the filing of the present invention or (2) which was known but whose biological activity was unknown at the time of the filing of the present invention, or a pharmaceutically acceptable salt thereof; or

[18-h] a FXa inhibitor containing as an effective component at least one compound identified or designed by, or a compound adapted for the method for conducting identification or molecular design of the inhibitor according to aspects [18-a] to [18-e], which has FXa inhibitory activity in terms of  $IC_{50}$  determined by a bioassay of up to 1  $\mu M$ , and (1) which was unknown at the time of the filing of the present invention or (2) which was known but whose FXa inhibitory activity was unknown at the time of the filing of the present invention, or a pharmaceutically acceptable salt thereof.

**[0080]** It should be noted that, the compound used in the aspects [18-f] to [18-h] is preferably the one having the FXa inhibitory activity in terms of  $IC_{50}$  of up to 0.5  $\mu M$ , more preferably up to 0.1  $\mu M$ , and most preferably up to 0.01  $\mu M$ .

**[0081]** In all of the aspects as described above, the expression "compound" should be deemed to also include "the pharmaceutically acceptable salt thereof".

**[0082]** The compound of the present invention may include an asymmetric carbon, and the compound of the present invention may be a mixture or an isolation product of geometric isomer, tautomer, optical isomer or other stereoisomer. Isolation or purification of such stereoisomer may be accomplished by those skilled in the art using any of the techniques commonly used in the art, for example, by optical resolution using preferential crystallization or column chromatography, or by asymmetric synthesis.

**[0083]** The compound (I) of the present invention may be in the form of an acid addition salt, and depending on the type of the substituent, the compound (I) may also be in the form of a salt with a base. Such salt is not particularly limited as long as the salt is a pharmaceutically acceptable salt, and exemplary salts include acid addition salts with hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, or other mineral acid; acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, formic acid, malic acid, tartaric acid, citric acid, mandelic acid, or other organic carboxylic acid; methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, 2-hydroxy ethanesulfonic acid, or other organic sulfonic acid; or aspartic acid, glutamic acid, or other acidic amino acid; and salts with a base of sodium, potassium, magnesium, calcium, aluminum or other alkaline metal or alkaline earth metal; methylamine, ethylamine, ethanolamine, pyridine, lysine, arginine, ornithine, or other organic base; and ammonium salt.

**[0084]** Furthermore, the salts of the compound of the present invention also include mono-salts, di-salts, and tri-salts. Still further, the compound of the present invention may simultaneously form an acid addition salt and a salt with base depending on the type of the substituent on the side chain.

**[0085]** Still further, the present invention also includes hydrates of the compound (I) as well as pharmaceutically acceptable solvates and crystalline polymorphic forms of the compound (I). It should also be taken for granted that the present invention is by no means limited to the compounds mentioned in the Examples as described below, and all of the tricyclic compounds having the spiro union as represented by formula (I) and their pharmaceutically acceptable salts are within the scope of the present invention.

**[0086]** It would be understood that such situation also applies to the compounds of the formulae (I'), (Im), (V), (VI), (Ik), (I-a'), (I''), (I'''), and the like.

[Production process]

**[0087]** The compounds of the present invention represented by formula (I) and the related compounds can be produced by the production processes as described below.

**[0088]** Unless otherwise noted, A, B, D, Q, T, X, Y, Z, l, m, n, and r in the compounds of formula (I), formula (I-a), formula (I-a'), formula (I-a-1), formula (I-a-2), formula (I-b), formula (Ik), formula (Ik'), formula (II), formula (II-a), formula (II-b), formula (II-c), formula (II-d), formula (II-e), formula (IIk), formula (II-1), formula (II-2), formula (II-3), formula (II-4), formula (II-5), formula (II-6), formula (II-7), formula (II-8), formula (II-9), formula (II-10), formula (II-11), formula (II-12), formula (III), formula (IIIk), formula (III-1), formula (III-2), formula (III-3), formula (III-4), formula (III-5), formula (IIIk-1), formula (IIIk-2), formula (IIIk-3), formula (IIIk-4), formula (IIIk-5), formula (IIIk-6), formula (IIIk-7), formula (IIIk-8), formula (IIIk-9), formula (IV), formula (V), and formula (VI) in the following <Production process 1>, <Production process

2>, <Production process 3>, and <Production process 4>, and their description, and their salts are as defined for formula (I). In the respective compounds described above, the side chains and the alkylene group in the rings are optionally substituted with the substituents defined for formula (I).

[0089] Unless otherwise noted, W in the production process represents the leaving group or the group convertible into the leaving group as described above. J represents a thiol protective group such as p-methoxybenzyl group. P<sub>1</sub> and P<sub>2</sub> in the intermediate compounds of formulae (Ik) to (IIIk-9) marked with "k" independently represent hydrogen atom or a protective group of the imino group (-NH-). Exemplary protective groups of the imino group (-NH-) include aralkyl groups such as benzyl group; acyl groups such as acetyl group; and alkoxycarbonyl groups such as benzyloxycarbonyl group, and t-butoxycarbonyl group. When P<sub>1</sub> and P<sub>2</sub> are protective groups of the imino group (-NH-), deblocking may be accomplished by adequately selecting the type of the protective groups or the conditions of the deblocking to independently or simultaneously remove the protective groups, and if necessary, the protective groups and the like can also be reintroduced.

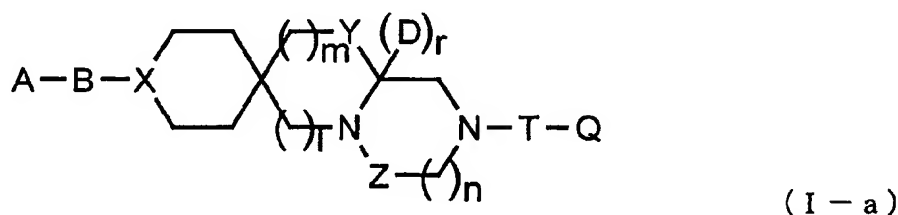
[0090] Unless otherwise noted, the reaction conditions employed in the production process are as described below. Reaction temperature is in the range of -78°C to the solvent-reflux temperature, and reaction time is the time sufficient for required progress of the reaction. Solvent which is not involved in the reaction may be any of the aromatic hydrocarbon solvents such as toluene and benzene; polar solvents such as water, methanol, DMF, and DMSO; basic solvents such as triethylamine and pyridine; halogen solvents such as chloroform, methylene chloride, and 1,2-dichloroethane; ethereal solvent such as diethylether, tetrahydrofuran, and dioxane; and mixed solvents thereof; and the solvent used may be adequately selected depending on the reaction conditions. Base may be any of inorganic bases such as potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, and sodium hydride; or organic bases such as triethylamine, pyridine, N,N-dialkylaniline, and lithium diisopropylamide; and acid may be any of mineral acids such as hydrochloric acid, and sulfuric acid; organic acids such as methanesulfonic acid and p-toluenesulfonic acid. The base and the acid are not necessarily limited to those mentioned above.

[0091] The compounds represented by formula (I) and formula (Ik) which are the compounds of the present invention or their salts may be synthesized from the compounds represented by formula (II), formula (IIk), formula (III), formula (IIIk), formula (III-3), formula (IIIk-4), formula (IIIk-6), formula (IV), formula (V), or formula (VI) or their salts which can be readily produced from known or commercially available compounds, by <Production process 1>, <Production process 2>, <Production process 3>, or <Production process 4>.

[0092] Next, the production process is described. The present invention, however, is by no means limited to the processes as described below.

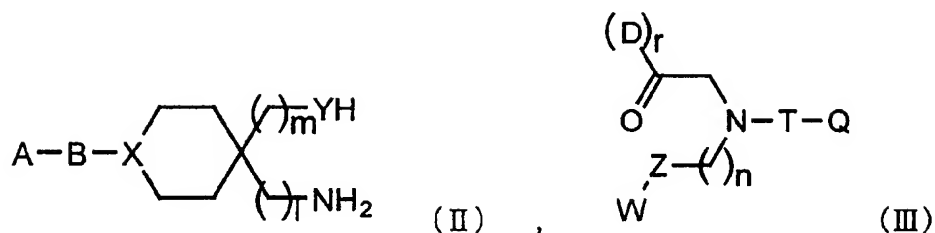
<Production process 1>

[0093] The compound represented by the formula:



(wherein A, B, D, Q, T, X, Y, Z, l, m, and n, and substitution of each alkylene chain are as defined above; and r is 1) or its salt may be produced by the process as described below.

[0094] Compounds represented by formula (II) and formula (III):

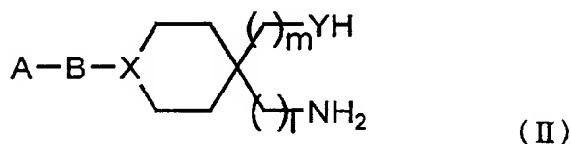


(wherein A, B, D, Q, T, X, Y, l, m, n, and W, and substitution of each alkylene chain are as defined above; r is 1; and Z represents carbonyl group or thiocarbonyl group) or their salts which are commercially available or readily derived from commercially available compounds may be reacted in accordance with the known process described in documents (for example, Journal of Medicinal Chemistry vol. 19, page 436, 1976; Journal of American Chemical Society vol. 107, page 7776, 1985; or Journal of Organic Chemistry vol. 63, page 1732, 1998) preferably by using toluene for the solvent in the presence or absence of an acid catalyst, and preferably, in the presence of p-toluenesulfonic acid. The reaction may be promoted at a temperature in the range of 0°C to the solvent reflux temperature, and preferably at the solvent reflux temperature for a time sufficient for the progress of the required reaction, and preferably for 2 to 6 hours to produce the compound represented by formula (I-a) or its salt. With regard to the substituent Z, interconversion between carbonyl group and thiocarbonyl group or conversion into methylene group may be accomplished, if necessary, by a known process, for example, by the process described in "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1817, 1978, Maruzen.

**[0095]** Next, typical processes for producing the compounds of formula (II) and formula (III) which are the starting compounds are described.

<1> Production process of the compound of formula (II):

**[0096]**



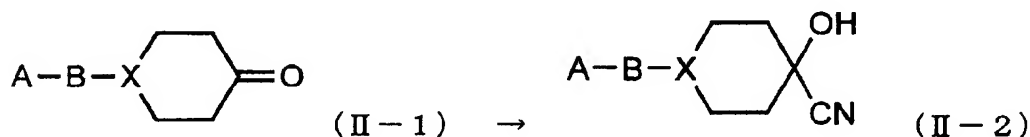
(In the formula, A, B, X, Y, l, and m, and substitution of each alkylene chain are as defined above.)

1-1) When l = 1 and m = 0

**[0097]** When Y is O (oxygen atom), the compound may be produced, for example, by the production process as described below.

<Step II-1-1>

**[0098]**

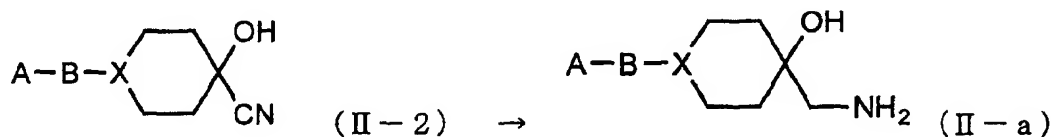


**[0099]** A compound represented by the formula (II-1) or its salt which is commercially available or readily derived from a commercially available compound may be reacted in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1455,

1978, Maruzen) to produce the compound represented by formula (II-2) or its salt.

<Step II-1-2>

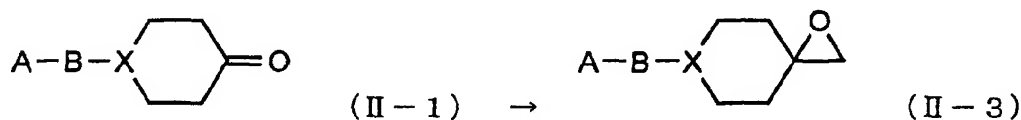
[0100] The compound represented by formula (II-2) or its salt obtained in <Step II-1-1> may be then reduced in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1332, 1978, Maruzen) to produce the compound represented by formula (II-a) or its salt.



[0101] Next, another process for producing the compound represented by formula (II-a) or its salt is described.

<Step II-2-1>

[0102] A compound represented by formula (II-1) or its salt may be reacted in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [I]", page 594, 1977, Maruzen) to produce the compound represented by formula (II-3) or its salt.



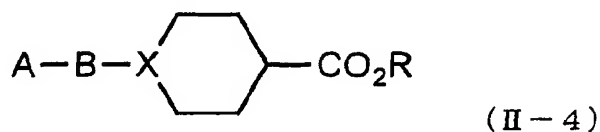
<Step II-2-2>

[0103] The compound represented by formula (II-3) or its salt obtained in <Step II-2-1> may be then reacted in accordance with the known process described in documents (for example, Synthesis, page 629, 1984) to produce the compound represented by formula (II-a) or its salt.

[0104] When Y is S (sulfur atom), the compound may be produced, for example, by the production process as described below.

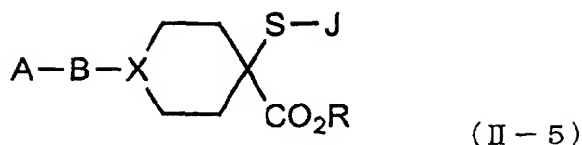
<Step II-3-1>

[0105]



[0106] A compound represented by the formula (II-4) (wherein R is a hydrocarbon group as typically represented by C<sub>1-6</sub> alkyl groups such as methyl, ethyl, propyl, and t-butyl and aralkyl groups such as benzyl group) or its salt which is commercially available or readily derived from a commercially available compound may be reacted in accordance with the known process described in documents (for example, JP09510700) to produce the compound represented

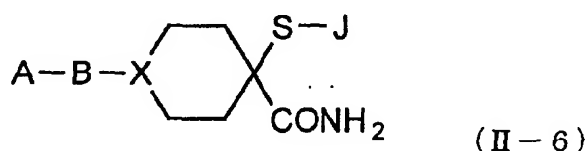
by formula (II-5):



(wherein R is the same as R in (II-4); J is a protective group such as p-methoxybenzyl group) or its salt.

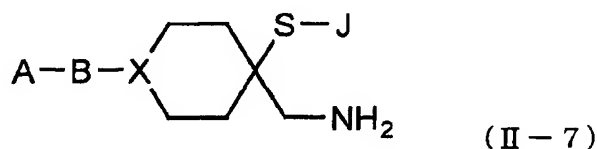
<Step II-3-2>

**[0107]** The compound represented by formula (II-5) or its salt obtained in <Step II-3-1> and ammonia or optionally protected amine are reacted for normal amidation to produce the compound represented by formula (II-6) or its salt.



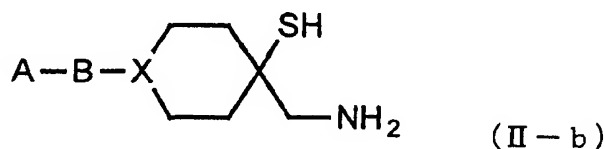
<Step II-3-3>

**[0108]** The compound represented by formula (II-6) or its salt obtained in <Step II-3-2> may be then reduced in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1332, 1978, Maruzen) to produce the compound represented by formula (II-7) or its salt.



<Step II-3-4>

**[0109]** The compound represented by formula (II-7) or its salt obtained in <Step II-3-3> may be then reacted for normal deblocking of the thiol protective group to produce the compound represented by formula (II-b) or its salt.

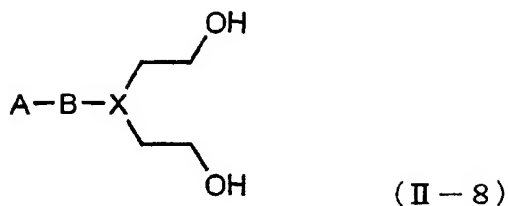


1-2) When l = 0, 1, or 2, and m = 1 or 2

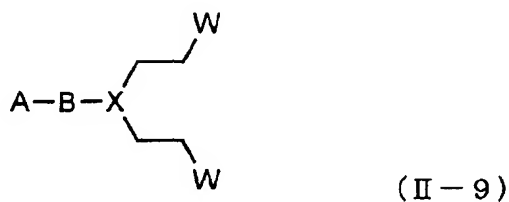
**[0110]** When Y is O (oxygen atom), the compound may be produced, for example, by the production process as described below.

&lt;Step II-4-1&gt;

[0111] A compound represented by formula (II-8):

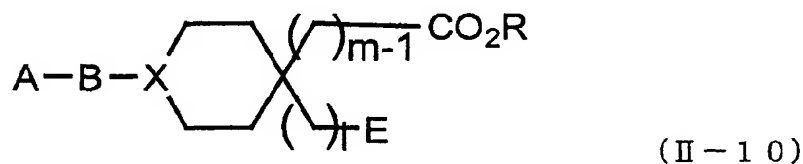


or its salt which is commercially available or readily derived from a commercially available compound may be reacted in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [I]", page 331, 1977, Maruzen) to produce a reactive derivative represented by formula (II-9) or its salt.



&lt;Step II-4-2&gt;

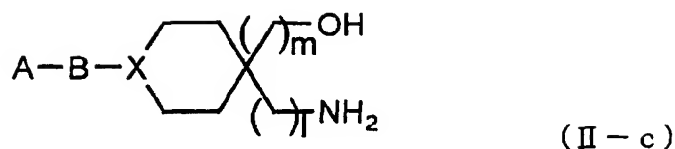
The compound represented by formula (II-9) or its salt obtained in <Step II-4-1> may be then reacted with an active methylene compound such as ethyl cyanoacetate, ethyl nitroacetate, ethyl malonate monoamide or ethyl cyanopropionate in a solvent which is not involved in the reaction in the presence of a base to produce the compound represented by formula (II-10) (wherein E represents nitro group, cyano group, or amide group; and R is the same as R defined in formula (II-4)) or its salt.



&lt;Step II-4-3&gt;

The compound represented by formula (II-10) or its salt obtained in <Step II-4-2> may be then reduced in accordance with the known process described in documents (for example, "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1332, 1978, Maruzen) to produce the compound represented by formula (II-c) or its salt.

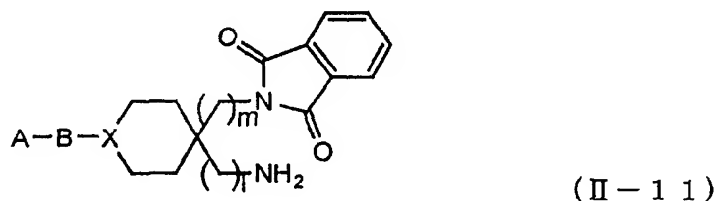




10 **[0114]** When Y is imino group (-NH-), the compound may be produced, for example, by the production process as described below.

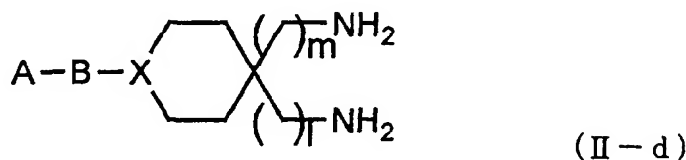
<Step II-5-1>

15 **[0115]** The compound represented by formula (II-c) or its salt obtained in <Step II-4-3> may be reacted with a phosphorus compound such as triphenylphosphin or tributylphosphin and an azodicarboxylate as typically represented by diethyl azodicarboxylate (DEAD) in a solvent which is not involved in the reaction to activate the hydroxyl group, and the resulting product may be reacted with phthalimide to produce the compound represented by formula (II-11) or its salt.



30 <Step II-5-2>

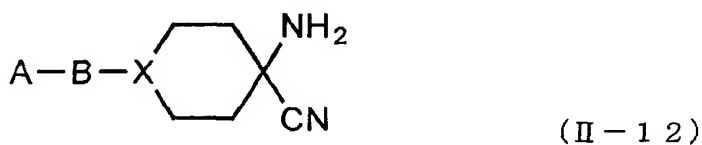
**[0116]** The compound represented by formula (II-11) or its salt obtained in <Step II-5-1> may be then reacted for deblocking to produce the compound represented by formula (II-d) or its salt.



45 **[0117]** When Y is imino group (-NH-), the compound may be produced, for example, by the alternative production process as described below.

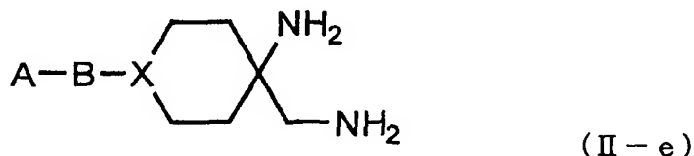
<Step II-6-1>

50 **[0118]** The compound represented by formula (II-2) or its salt may be reacted in accordance with the known process described in documents (for example, "Synthesis", page 832, Scheme 2, 1994) to produce the compound represented by formula (II-12) or its salt.



<Step II-6-2>

[0119] The compound represented by formula (II-12) or its salt obtained in <Step II-6-1> may be reduced in accordance with <Step II-1-2> to produce the compound represented by formula (II-e) or its salt.



[0120] Next, another process for producing the compound represented by formula (II-12) or its salt is described.

<Step II-6-3>

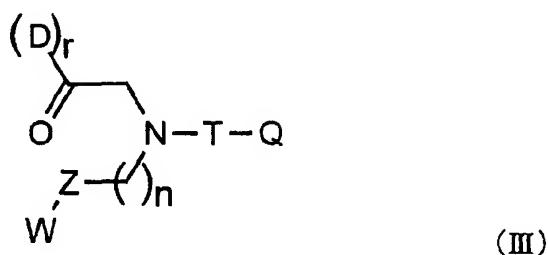
[0121] The compound represented by formula (II-1) or its salt may be reacted in accordance with the known process described in documents (for example, DE4405140, Scheme 1 (Reaction i)) to produce the compound represented by formula (II-12) or its salt.

[0122] In the foregoing steps, the substituent may be introduced into the alkylene chain, for example, by using a commercially available compound having the corresponding substituent for the starting material (II-1) or (II-8); by introducing the corresponding substituent in the starting material by the process commonly used in the synthesis; by converting the active methylene compound of <Step II-4-1> to an adequately substituted derivative before the reaction with the methylene compound; by reducing the cyano group in (II-2) or (II-4) to amide group, and converting and/or modifying the carbonyl group as desired; or if necessary, by directly introducing the substituent into the compound represented by formula (II).

[0123] With regard to the preferable substituent D, D may be introduced in accordance with the process employed for the synthesis of D as described below.

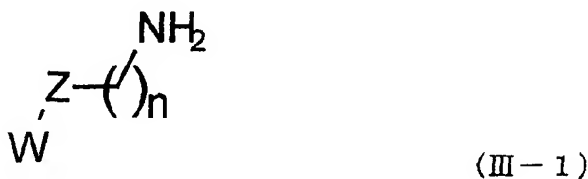
<2> Production process of the compound of formula (III):

[0124]



<Step III-1-1>

[0125] A compound represented by formula (III-1):

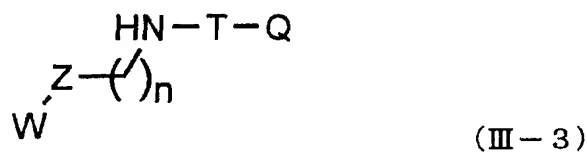


(wherein n is 1 or 2) or its salt which is commercially available or readily derived from a commercially available compound, and a compound represented by formula (III-2):

W-T-Q

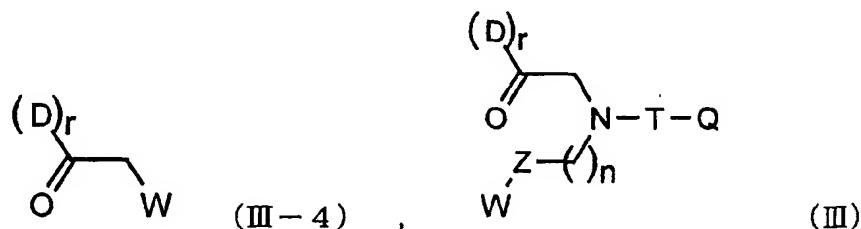
(III-2)

(wherein W, Q, and T are as described above) or its salt which is commercially available or readily derived from a commercially available compound may be fused to produce the compound represented by formula (III-3) or its salt. When T is sulfonyl group and W is chlorine atom, for example, the reaction may be carried out in methylene chloride in the presence of triethylamine at a temperature in the range of 0°C to room temperature, and preferably, at room temperature for 2 to 12 hours.



&lt;Step III-1-2&gt;

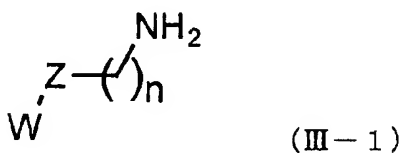
**[0126]** The compound represented by formula (III-3) or its salt obtained in <Step III-1-1> may be reacted with an alkylating agent represented by formula (III-4) in a solvent which is not involved in the reaction in the presence of a base to produce the compound represented by formula (III) or its salt.



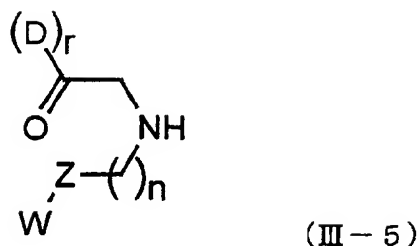
**[0127]** Next, another process for producing the compound represented by formula (III) or its salt is described.

&lt;Step III-2-1&gt;

**[0128]** A commercially available compound represented by formula (III-1):

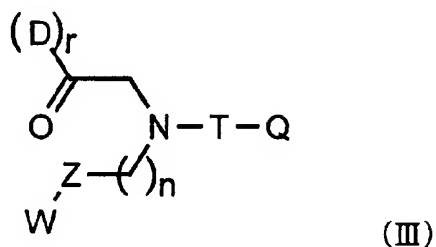


(wherein n is 1 or 2) or its salt is reacted in accordance with the procedure of <Step III-1-2> to produce the compound represented by formula (III-5) or its salt.



<Step III-2-2>

**[0129]** The compound represented by formula (III-5) or its salt obtained in <Step III-2-1> is condensed with the compound represented by formula (III-2) or its salt in accordance with the procedure of <Step III-1-1> to produce the compound represented by formula (III) or its salt.

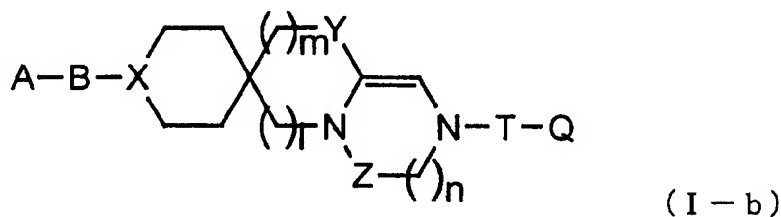


**[0130]** It should be noted that the carbonyl group in the formula (III) may be protected if necessary, and the protective group may be removed at an adequate stage.

**[0131]** In the steps of producing the compound of formula (III), substituent may be introduced at the alkylene chain, for example, by using a commercially available compound having the corresponding substituent for the starting material (III-1) or (III-4); or by introducing the corresponding substituent in the starting material by the known process described in the documents.

<Production process 2>

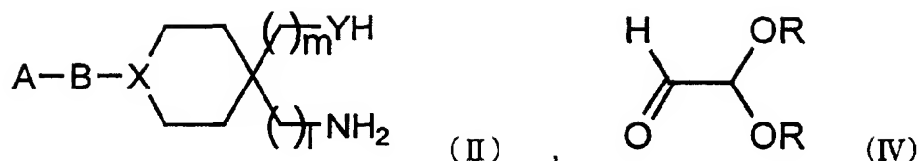
**[0132]** The compound represented by:



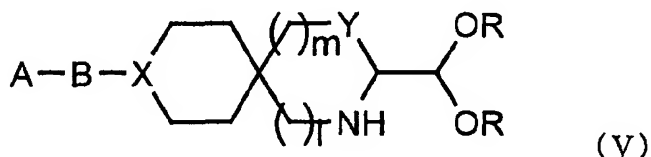
(wherein A, B, Q, T, X, Y, Z, l, m, and n are as defined above) or its salt may be produced by the process as described below.

<Step 1>

**[0133]** The compound represented by formula (II) produced by the process described in <Production process 1> or its salt and the compound represented by formula (IV) or its salt which is commercially available or readily derived from a commercially available compound



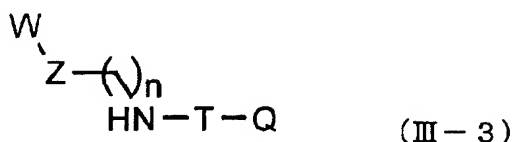
(wherein A, B, X, Y, l, and m, and substitution of each alkylene chain are as defined above; and R is hydrogen atom, a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a C<sub>1-6</sub> alkyl group optionally substituted with hydroxyl or a halogen atom (and in particular, methyl group or ethyl group); or the two R may together represent a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, a C<sub>2-4</sub> alkylene group optionally substituted with hydroxyl or a halogen atom (in particular, 1,2-ethylene group or 1,3-propylene group)) may be reacted in accordance with the procedure of <Production process 1> to produce the compound represented by formula (V) or its salt.



(In the formula, A, B, X, Y, l, and m, and substitution of each alkylene chain are as defined above; and R is the same as R defined in formula (IV).)

<Step 2>

**[0134]** The compound represented by formula (V) or its salt obtained in <Step 1> and the compound represented by formula (III-3):



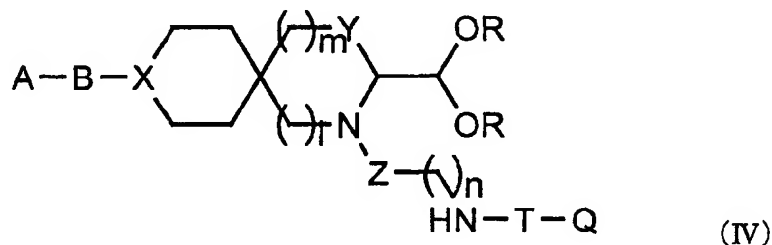
(wherein Q, T, W, Z, and n, and substitution of each alkylene chain are as defined above) or its salt prepared by the procedure described in <Production process 1> may be reacted to produce the compound represented by formula (VI) or its salt.

**[0135]** When Z is carbonyl group or thiocarbonyl group, and W is a halogen atom, hydroxyl group, or an alkoxy group in the compound represented by formula (III-3) or its salt, amidation in normal peptide is carried out. For example, when W is hydroxyl group, a phenol such as 2,4,5-trichlorophenol, pentachlorophenol, 2-nitrophenol, or 4-nitrophenol, or a N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxy-5-norbornene-endo-2,3-dicarboxyimide or N-hydroxypiperidine is condensed in the presence of a condensing agent such as N,N-dicyclohexylcarbodiimide for conversion into active ester form, and allowed for reaction.

**[0136]** Alternatively, the reaction may be conducted after producing a mixed acid anhydride by reacting with a halogenated acyl compound such as isobutylchloroformate. The reaction may be also promoted by using a peptide condensation reagent such as N,N-dicyclohexylcarbodiimide, diphenylphosphoric acid azide or diethyl cyanophosphate alone.

**[0137]** When Z is methylene group in the compound represented by formula (III-3) or its salt, normal N-alkylation may be promoted in a solvent which is not involved in the reaction to produce the compound represented by formula (VI) or its salt.

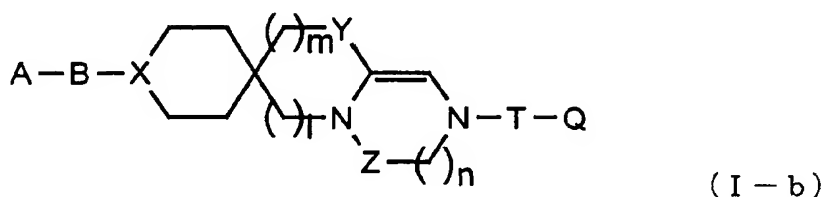
[0138] Furthermore, when W is hydroxyl group, the compound represented by formula (III-3) may be activated by using a phosphorus compound such as triphenylphosphin or tributylphosphin and an azodicarboxylate typically represented by diethyl azodicarboxylate, and then reacted in a solvent which is not involved in the reaction.



(In the formula, A, B, Q, T, X, Y, Z, l, m, and n, and substitution of each alkylene chain are as defined above. R is the same as R defined in formula (IV).)

<Step 3>

[0139] The compound represented by formula (VI) (wherein A, B, Q, T, X, Y, Z, l, m, and n, and substitution of each alkylene chain are as defined above; and R is the same as R defined in the compound represented by formula (IV)) or its salt obtained in <Step 2> may be then reacted in accordance with the known process described in documents (for example, JP09316059) in a solvent which is not involved in the reaction, and preferably by using toluene for the solvent, in the presence of an acid catalyst, and preferably in the presence of p-toluenesulfonic acid to produce a compound represented by formula (I-b) or its salt. The reaction temperature is preferably in the range of 70°C to 80°C, and the reaction time is preferably in the range of 1 to 2 hours. With regard to the substituent Z, interconversion between carbonyl group and thiocarbonyl group or conversion into methylene group may be accomplished, if necessary, by a known process, for example, the process described in "Shinjikkenkagakukouza 14 Synthesis and Reaction of Organic Compounds [III]", page 1817, 1978, Maruzen.

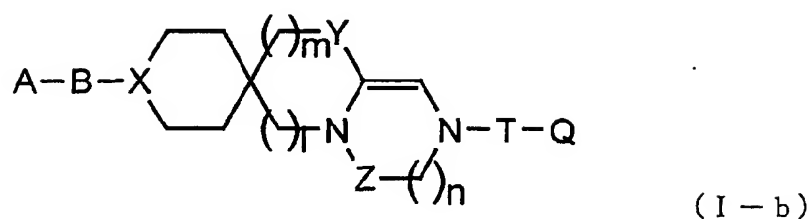


(In the formula, A, B, Q, T, X, Y, Z, l, m, and n are as defined above)

<Production process 3>

[0140] Another process for producing a compound represented by formula (I-a) or its salt is as described below.

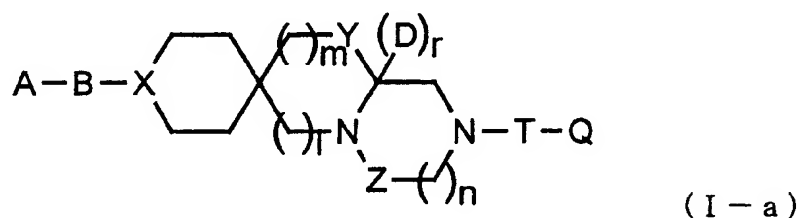
[0141] The compound represented by formula (I-b):



(wherein A, B, Q, T, X, Y, Z, I, m, and n are as defined above) or its salt produced in <Production process 2> may be reacted for reduction of the double bond in the formula to produce the compound represented by formula (I-a) or its salt. Exemplary reduction processes include reduction by a metal or a metal salt such as sodium, calcium and aluminum; reduction by a metal hydride such as diisopropyl aluminum hydride; and reduction by a metal hydride complex such as sodium borohydride; electrophilic reduction by diborane or substituted borane; and catalytic hydrogenation using a metal catalyst. The reaction solvents used is a solvent which is not involved in the reaction, for example, tetrahydrofuran, toluene, methylene chloride, or methanol, or a mixture thereof, and the reaction is conducted at a temperature of -78°C to reflux temperature for a time sufficient for required progress of the reaction.

15

20

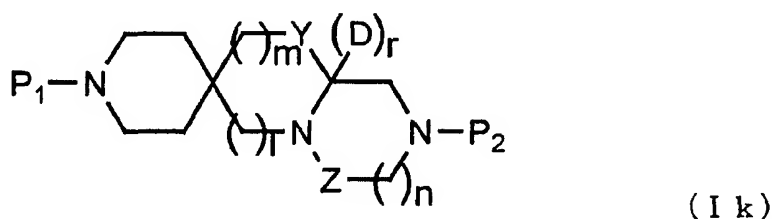


(In the formula, A, B, D, Q, T, X, Y, Z, I, m, n, and r are as defined above)

<Production process 4>

35

**[0142]** The compound represented by formula:



(wherein D, P<sub>1</sub>, P<sub>2</sub>, Y, Z, I, m, n, and r, and substitution of each alkylene chain are as defined above) or its salt may be produced by the process as described below.

50

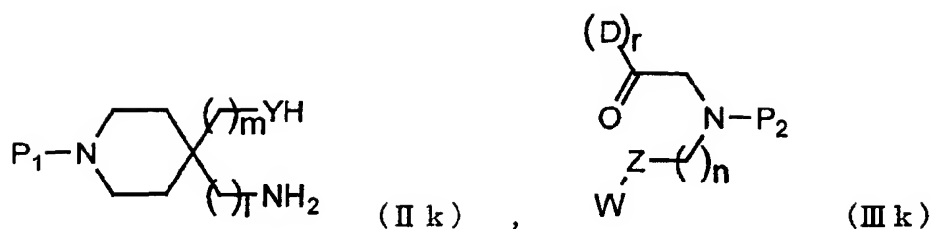
<1> Production process of the compound of formula (Ik)

(Skeleton forming reaction)

<Step 1>

55

**[0143]** Compounds represented by formula (IIk) and formula (IIIk):

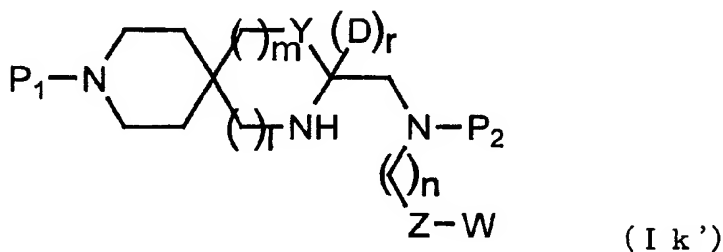


(wherein D, P<sub>1</sub>, P<sub>2</sub>, W, Y, Z, I, m, and n, and substitution of each alkylene chain are as defined above; and r is 1) or their salts which are commercially available or readily derived from a commercially available compound may be reacted in accordance with <Production process 1> to produce a compound represented by formula (Ik) or its salt.

15 **[0144]** The compound represented by formula (Ik) or its salt may be produced also by another process as described below.

<Step 2>

20 **[0145]** The reaction may be promoted in accordance with <Step 1> by using a reaction solvent which is described in <Production process 1>, or alternatively, a halogen solvent such as methylene chloride, chloroform, or 1,2-dichloroethane, the preferred being chloroform, and there is produced a compound of formula (Ik') (wherein D, P<sub>1</sub>, P<sub>2</sub>, W, Y, Z, I, m, and n, and substitution of each alkylene chain are as defined above; and r is 1).



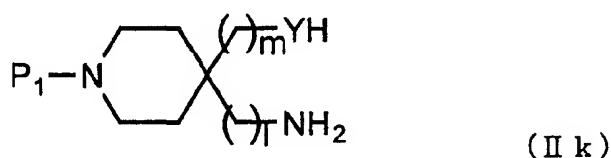
35 <Step 3>

**[0146]** The compound represented by formula (Ik') or its salt produced in <Step 2> may be then condensed in accordance with <Production process 2> <Step 2> to produce the compound represented by formula (Ik) or its salt.

40 **[0147]** Next, typical production processes of the compounds of formula (Ik) and formula (IIIk) which are the starting compounds are described.

<2> Production process of the compound of formula (IIk)

45 **[0148]**



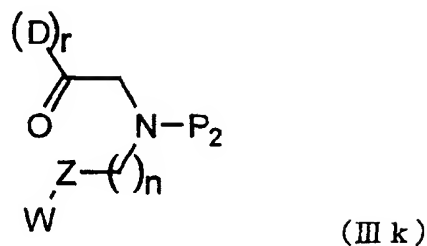
55 (In the formula, P<sub>1</sub>, Y, I, and m, and substitution of each alkylene chain are as defined above.)

**[0149]** The compound represented by formula (IIk) or its salt may be produced in accordance with the production process of <Production process 1> <formula (II)>.



<3> Production process of the compound of formula (IIIk)

[0150]



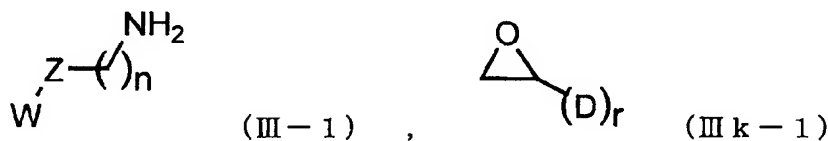
(In the formula, D, P<sub>2</sub>, W, Z, and n, and substitution of each alkylene chain are as defined above; and r is 1.)

[0151] The compound represented by formula (IIIk) or its salt may be produced in accordance with the production process of <Production process 1> <formula (III)>.

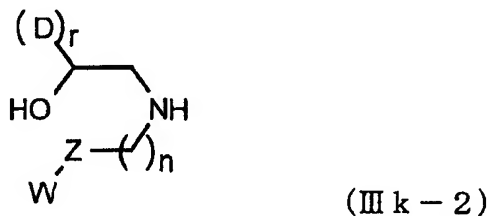
[0152] The compound represented by formula (IIIk) may be produced also by different processes as described below.

<Step IIIk-1-1>

[0153] The compounds represented by formula (III-1) and formula (III k - 1):

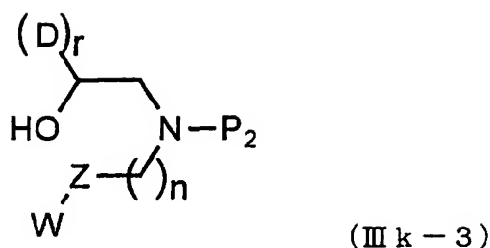


(wherein n is 1 or 2) or their salts which are commercially available or readily derived from a commercially available compound may be reacted for nucleophilic addition associated with ring opening of the epoxide to produce the compound represented by formula (IIIk-2) or its salt.



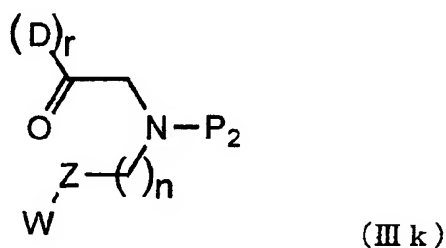
<Step IIIk-1-2>

[0154] The compound represented by formula (IIIk-2) or its salt obtained in <Step IIIk-1-1> may be then reacted for normal introduction of the protective group P<sub>2</sub> into the imino group (-NH-) to produce the compound represented by formula (IIIk-3) or its salt.



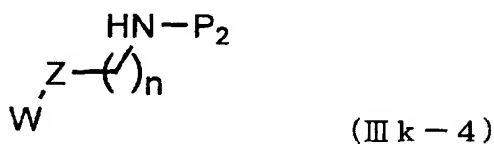
<Step IIIk-1-3>

**[0155]** The compound represented by formula (IIIk-3) or its salt obtained in <Step IIIk-1-2> may be then reacted in a solvent which is not involved in the reaction for oxidation by manganese dioxide; chromic acid oxidation by chromium oxide (VI) or dichromate; oxidation by lead tetraacetate; oxidation by oxygen; oxidation by activated DMSO; oxidation by high valence iodine typically represented by Dess-Martin reagent; oxidation by halogen compound such as hypohalogenous acid or its salt to produce the compound represented by formula (IIIk) or its salt.



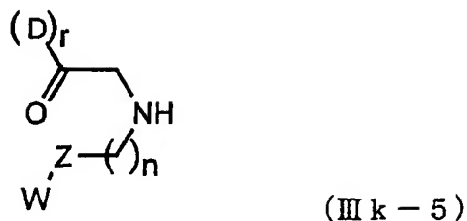
<Step IIIk-2-1> and <Step IIIk-2-2>

**[0156]** Alternatively, the compound represented by formula (III-1) or its salt may be reacted by <Step IIIk-1-2> and <Step IIIk-1-1> through the compound represented by formula (IIIk-4) or its salt to produce the compound represented by formula (IIIk-3) or its salt.



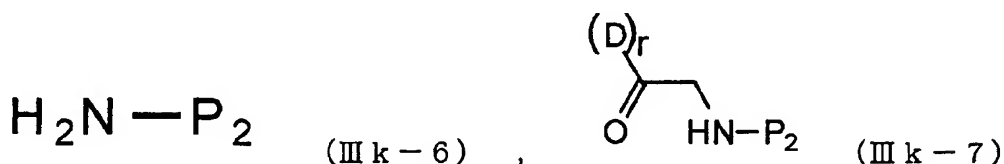
<Step IIIk-3-1> and <Step IIIk-3-2>

**[0157]** Alternatively, the compound represented by formula (IIIk-2) or its salt may be reacted by <Step IIIk-1-3> and <Step IIIk-1-2> through the compound represented by formula (IIIk-5) or its salt to produce the compound represented by formula (IIIk) or its salt.



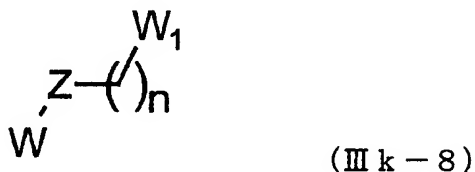
10 <Step IIIk-4-1>

15 **[0158]** The compound represented by formula (IIIk-6) or its salt which is commercially available or readily derived from a commercially available compound may be reacted in accordance with <Production process 1> <Step III-1-2> to produce the compound represented by formula (IIIk-7) or its salt.



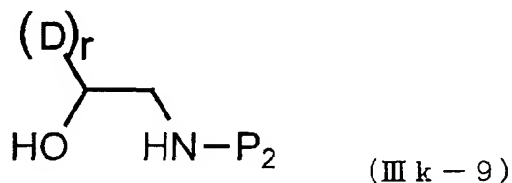
25 <Step IIIk-4-2>

**[0159]** The compound represented by formula (IIIk-7) or its salt obtained in <Step IIIk-4-1> and the compound represented by formula (IIIk-8):



40 (wherein W, Z, and n are as defined above; and W<sub>1</sub> is a group selected from the groups defined for W for selective substitution of W<sub>1</sub> in this reaction) or its salt which is commercially available or readily derived from a commercially available compound may be then condensed in accordance with the procedure of <Step IIIk-4-1> to produce the compound represented by formula (IIIk) or its salt. <Step IIIk-5-1>, <Step IIIk-5-2> and <Step IIIk-5-3>

45 **[0160]** Alternatively, the compound represented by formula (IIIk-6) or its salt may be reacted in accordance with <Step IIIk-1-1> and <Step IIIk-1-2> through the compound represented by formula (IIIk-9) or its salt to produce the compound represented by formula (IIIk-3) or its salt. Alternatively, the compound of formula (IIIk-9) may be oxidized in accordance with <Step IIIk-1-3> to produce the compound represented by formula (IIIk-7) or its salt.

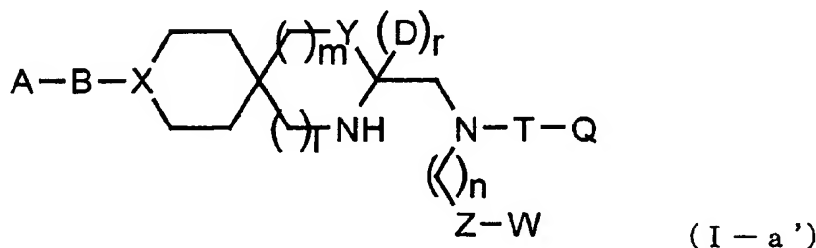


**[0161]** Alternatively, a compound having -T-Q instead of the -P<sub>2</sub>, for example, a compound of formula (IIIk-6) wherein

-P<sub>2</sub> is -T-Q, or a compound of formula (III-4) wherein -P<sub>2</sub> is -T-Q may be used in accordance with the alternative process as described above to produce the compound represented by formula (II) or its salt.

[0162] In the <Production process 4>, P<sub>1</sub> or P<sub>2</sub> may be independently deblocked at the most adequate stage for subsequent conversion into the A-B or the T-Q. Conversion into the A-B and the T-Q is described later.

[0163] Furthermore, when the <Production process 4> is adopted, the compound represented by formula (I-a) or its salt wherein P<sub>1</sub> is A-B-, and -P<sub>2</sub> is -T-Q can be produced by the production of the compound represented by formula (I-a')



(wherein A, B, D, Q, T, X, Y, I, m, n, and W, and substitution of each alkylene chain are as defined above; r is 1; and Z represents carbonyl group or thiocarbonyl group) or its salt followed by condensation.

[0164] In the foregoing, production process of the skeleton of the compound of the present invention has been described in detail.

[0165] Next, conversion of the substituents D, A-B, and T-Q is described.

[0166] The conversion of the substituents D, A-B, and T-Q may be carried out at any stage in the <Production process 1>, <Production process 2>, <Production process 3>, and <Production process 4>, or in the stage of the starting compound, or in any reaction stage of producing such starting compound.

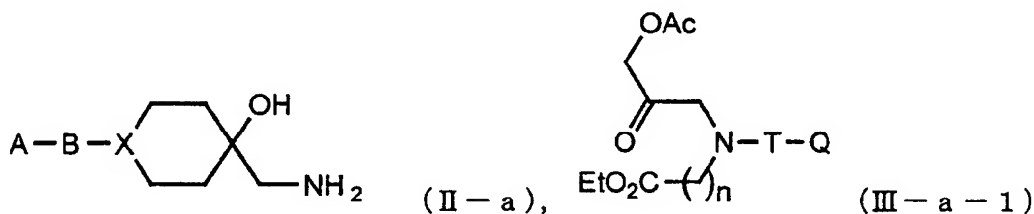
[0167] In the synthesis of the compound of the present invention (I), those skilled in the art can choose the best timing for the substituent conversion.

[0168] Typical conversion process of the substituents D, A-B, and T-Q are described in the following section which by no means limit the scope of the invention.

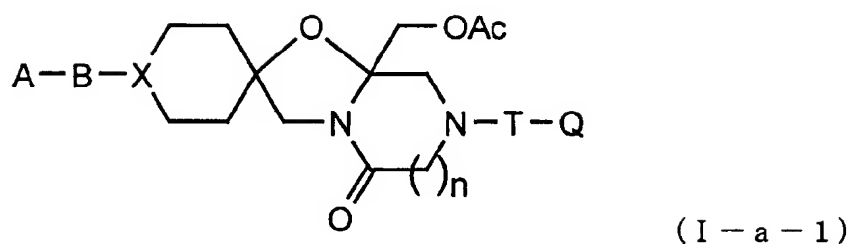
[0169] For example, the conversion of the substituent D is conducted as described below (for the case wherein m = 1) when the compound represented by formula (I-a) or its salt is employed.

<Step D-1>

[0170] The compounds represented by formula (II-a) and formula (III-a-1):



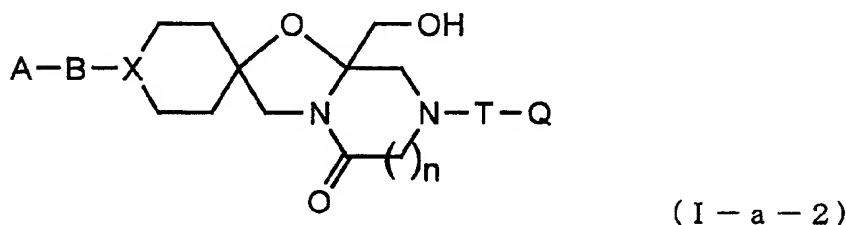
(wherein A, B, Q, T, X, and n, and substitution of each alkylene chain are as defined above; and Ac represents acetyl group) or their salts prepared by the procedure described in <Production process 1> were reacted in accordance with <Production process 1> to produce the compound represented by formula (I-a-1):



(wherein A, B, Q, T, X, n, and Ac, and substitution of each alkylene chain are as defined above) or its salt.

15 <Step D-2>

**[0171]** The compound represented by formula (I-a-1) or its salt obtained in <Step D-1> is reacted with aqueous solution of sodium hydroxide, for example, in methanol at room temperature to produce the compound represented by formula (I-a-2):



(wherein A, B, Q, T, X, and n, and substitution of each alkylene chain are as defined above) or its salt.

**[0172]** Next, typical production process for converting the side chain from an adequate precursor D', for example, the D' which is -CH<sub>2</sub>OH (as in the case of the compound of formula (I-a-2)) to the substituent D is described.

35 1) Substituent D convertible from D' which is -CH<sub>2</sub>OH

1-1) Production of a compound wherein D is -CH<sub>2</sub>-OR'

(wherein R' is an optionally substituted C<sub>1-6</sub> alkyl group) or its salt

1-1-1) Production process using R'-W

**[0173]** The compound wherein D' is -CH<sub>2</sub>OH or its salt may be reacted with a compound represented by formula: R'-W in a solvent which is not involved in the reaction, and preferably, in the mixed solvent of methylene chloride and water in the presence of a base, and preferably, using sodium hydroxide in the presence or absence of a phase transfer catalyst such as quaternary ammonium salt or crown ether, and preferably, in the presence of benzytriethylammonium chloride at a temperature of -78°C to reflux temperature, and preferably, at 0°C for a time sufficient for the required progress of the reaction, and preferably, for 2 hours for conversion into the compound wherein D is -CH<sub>2</sub>-OR' or its salt.

45 1-1-2) Production process using R'-OH

**[0174]** The compound wherein D' is -CH<sub>2</sub>OH or its salt is reacted with a compound represented by formula: R'-OH activated by using a phosphorus compound such as triphenylphosphine or tributylphosphine and an azodicarboxylate as typically represented by diethyl azodicarboxylate (DEAD) in a solvent which is not involved in the reaction for conversion into the compound wherein D is -CH<sub>2</sub>-OR' or its salt.

50 1-2) Production of a compound wherein D is -CH<sub>2</sub>-O-CO-R''

(wherein R'' is an optionally substituted C<sub>1-6</sub> alkyl group) or its salt

**[0175]** The compound wherein D' is -CH<sub>2</sub>OH or its salt may be reacted with R''-CO-W in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid for conversion into the compound wherein D is -CH<sub>2</sub>-O-CO-R'' or its salt.

55 1-3) Production of a compound wherein D is -CH<sub>2</sub>-NR'R'' (wherein -NR' and R'' are an amino group represented, for example, by -NR<sub>6</sub>R<sub>7</sub> (wherein R<sub>6</sub> and R<sub>7</sub> are independently hydrogen atom, a C<sub>1-6</sub> alkyl, a C<sub>4-7</sub> cycloalkyl, or a C<sub>2-6</sub> alkenyl; or R<sub>6</sub>, R<sub>7</sub> and the nitrogen to which they are binding together represent a five- to seven-membered heterocyclic ring wherein the heterocyclic ring contains 1 to 2 heteroatoms selected from N, S, and O; said R<sub>6</sub> and R<sub>7</sub> being optionally

further substituted with an adequate substituent)) or its salt

**[0176]** The compound wherein D' is  $-\text{CH}_2\text{OH}$  or its salt may be reacted with thionyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride, or the like in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid for conversion into the compound wherein D' is  $-\text{CH}_2-\text{W}$  or its salt.

5 The compound wherein D' is  $-\text{CH}_2-\text{W}$  or its salt may be further reacted with an amine represented by  $\text{HNR}'\text{R}''$  (for example,  $\text{HNR}_6\text{R}_7$  and  $\text{NR}_6\text{R}_7$  are as defined above) in a solvent which is not involved in the reaction in the presence or absence of copper powder, copper oxide powder, or iron powder in the presence or absence of a base or in the presence or absence of an acid for conversion into the compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}''$  or its salt. If necessary, a metal such as copper, palladium, chromium, or bismuth may be employed for formation of a complex with the compound

10 wherein D' is represented by  $-\text{CH}_2-\text{W}$  in order to use the compound with a higher activity in the reaction.

**[0177]** Alternatively, the compound wherein D' is  $-\text{CH}_2\text{OH}$  or its salt may be reacted with a phosphorus compound such as triphenylphosphin or tributylphosphin and an azodicarboxylate as typically represented by diethyl azodicarboxylate (DEAD) in a solvent which is not involved in the reaction to activate the hydroxyl group, and the resulting product may be reacted with the compound represented by formula:  $\text{NHR}'\text{R}''$  for conversion into the compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}''$  or its salt.

15

**[0178]** When R'' is hydrogen in the resulting compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}''$  or its salt, the compound may be reacted with  $\text{R}'''-\text{CO}-\text{W}$  (wherein W is as defined above; and R''' is an optionally substituted  $\text{C}_{1-6}$  alkyl group) in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid for conversion into the compound wherein D is  $-\text{CH}_2-\text{NR}'-\text{CO}-\text{R}'''$  or its salt. When the reaction is proceeded by using  $\text{R}'''-\text{S}(\text{O})_z-\text{W}$  (wherein W, R''', and z are as defined above) instead of the  $\text{R}'''-\text{CO}-\text{W}$ , the compound can be converted into the compound wherein D is  $-\text{CH}_2-\text{NR}'-\text{S}(\text{O})_z-\text{R}'''$  or its salt.

20

**[0179]** When R'' is hydrogen in the resulting compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}''$  or its salt, the compound may be also alkylated with  $\text{R}'''-\text{W}$  (wherein R''' is an optionally substituted  $\text{C}_{1-6}$  alkyl group) in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid for conversion into the compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}'''$  or its salt.

25

**[0180]** When R'' is hydrogen in the resulting compound wherein D is  $-\text{CH}_2-\text{NR}'\text{R}''$  or its salt, the compound may be also reacted with a ketone or an aldehyde represented by formula:  $\text{R}_{d1}-\text{CO}-\text{R}_{d2}$  (wherein  $\text{R}_{d1}$  and  $\text{R}_{d2}$  are independently hydrogen atom, an optionally substituted  $\text{C}_{1-6}$  alkyl group, a  $\text{C}_{3-6}$  cycloalkyl group, or a five- or six-membered heterocyclic group containing at least one heteroatom selected from N, O, and S, or d1, d2 and carbon atom of the ketone together form a five- or six-membered cyclic group which may contain at least one heteroatom selected from N, O, and S) in a solvent which is not involved in the reaction in the presence of a reducing agent such as sodium borohydride, lithium aluminum hydride, or diisobutylaluminum hydride for reductive amination of the compound to thereby convert the compound into the compound wherein D is  $-\text{CH}_2-\text{NR}'-\text{CHR}_{d1}\text{R}_{d2}$  or its salt.

30

1-4) Production of a compound wherein D is  $-\text{CHO}$  or its salt

**[0181]** The compound wherein D' is  $-\text{CH}_2\text{OH}$  or its salt may be reacted in a solvent which is not involved in the reaction for oxidation by manganese dioxide; chromic acid oxidation by chromium oxide (VI) or dichromate; oxidation by lead tetraacetate; oxidation by oxygen; oxidation by activated DMSO; oxidation by halogen compound such as hypohalogenous acid or its salt to thereby convert the compound into the compound wherein D is  $-\text{CHO}$  or its salt.

35

1-5) Production of a compound wherein D is  $-\text{CO}_2\text{H}$  or its salt

**[0182]** The compound wherein D' is  $-\text{CH}_2\text{OH}$  or its salt may be reacted in a solvent which is not involved in the reaction for oxidation by manganese dioxide; chromic acid oxidation by chromium oxide (VI) or dichromate; oxidation by lead tetraacetate; oxidation by oxygen; oxidation by activated DMSO; oxidation by halogen compound such as hypohalogenous acid or its salt to thereby convert the compound into the compound wherein D is  $-\text{CO}_2\text{H}$  or its salt.

40

**[0183]** The compound wherein D is  $-\text{CO}_2\text{H}$  or its salt can be also produced by reacting the compound wherein D is  $-\text{CHO}$  or its salt synthesized in 1-4) for oxidation by manganese dioxide; chromic acid oxidation by chromium oxide (VI) or dichromate; oxidation by lead tetraacetate; oxidation by oxygen; oxidation by activated DMSO; oxidation by halogen compound such as hypohalogenous acid or its salt.

45

2) Substituent D convertible from D which is  $-\text{CHO}$

2-1) Production of the compound wherein D is  $-\text{CH}(\text{OH})-\text{R}_{d3}$  (wherein  $\text{R}_{d3}$  is an adequate group selected from the  $\text{R}_{15}$  defined for D) or its salt

50

**[0184]** The compound wherein D is  $-\text{CHO}$  or its salt synthesized in 1-4) may be reacted with a nucleophilic reagent such as methylolithium or phenyllithium in a solvent which is not involved in the reaction for conversion into the compound wherein D is  $-\text{CH}(\text{OH})\text{R}_{d3}$  or its salt.

**[0185]** The resulting compound wherein D is  $-\text{CH}(\text{OH})\text{R}_{d3}$  or its salt may be converted into the compound wherein D is  $-\text{CH}(\text{OR}')\text{R}_{d3}$  or its salt by the procedure similar to 1-1); into the compound wherein D is  $-\text{CH}(\text{O}-\text{CO}-\text{R}')\text{R}_{d3}$  or its salt by the procedure similar to 1-2); and into the compound wherein D is  $-\text{CH}(\text{NR}'\text{R}'')\text{R}_{d3}$  (wherein  $\text{NR}'\text{R}''$  is as defined above) or its salt by the procedure similar to 1-3).

55

**[0186]** The compound wherein D is  $-\text{CH}(\text{OH})\text{R}_{d3}$  or its salt may be also converted into the compound wherein D is

-CO-R<sub>d4</sub> (wherein R<sub>d4</sub> is an alkyl group adequately selected from for example R<sub>15</sub>) by the procedure similar to 1-4). The resulting compound wherein D is -CO-R<sub>d4</sub> or its salt may be reacted with an alkylidene phosphorane represented by formula: Ph<sub>3</sub>P=CR<sub>d5</sub>R<sub>d6</sub> in a solvent which is not involved in the reaction for conversion into the compound wherein D is -CR<sub>d4</sub>=CR<sub>d5</sub>R<sub>d6</sub> or its salt. The compound wherein D is -CR<sub>d4</sub>=CR<sub>d5</sub>R<sub>d6</sub> or its salt may be hydrogenated by using a catalyst such as activated carbon-palladium to convert the compound into the compound wherein D is -CHR<sub>d4</sub>-CHR<sub>d5</sub>R<sub>d6</sub> (wherein R<sub>d5</sub> and R<sub>d6</sub> are, for example, a C<sub>1-6</sub> alkyl group) or its salt.

2-2) Production of the compound wherein D is -CH=CR<sub>d5</sub>R<sub>d6</sub> or its salt

**[0187]** The compound wherein D is -CHO or its salt synthesized in 1-4) may be reacted with an alkylidene phosphorane represented by formula: Ph<sub>3</sub>P=CR<sub>d5</sub>R<sub>d6</sub> in a solvent which is not involved in the reaction for conversion into the compound wherein D is -CH=CR<sub>d5</sub>R<sub>d6</sub> or its salt.

**[0188]** The resulting compound wherein D is -CH=CR<sub>d5</sub>R<sub>d6</sub> or its salt may be hydrogenated by using a catalyst such as activated carbon-palladium in a solvent which is not involved in the reaction to convert the compound into the compound wherein D is -CH<sub>2</sub>-CHR<sub>d5</sub>R<sub>d6</sub> or its salt.

2-3) Production of the compound wherein D is -CH-NR'R'' or its salt

**[0189]** The compound wherein D is -CHO or its salt synthesized in 1-4) may be reacted with the amine represented by the formula: HNR'R'' as described above in a solvent which is not involved in the reaction in the presence of a reducing agent such as sodium borohydride, lithium aluminum hydride, or diisobutylaluminum hydride for reductive amination to thereby convert the compound into the compound wherein D is -CH-NR'R'' or its salt.

3) Substituent D convertible from D which is -CO<sub>2</sub>H

3-1) Production of the compound wherein D is -CO<sub>2</sub>R' or its salt

**[0190]** The compound wherein D is -CO<sub>2</sub>H or its salt synthesized in 1-5) may be reacted with R'-OH (wherein R' is an optionally substituted C<sub>1-6</sub> alkyl group) in a solvent which is not involved in the reaction in the presence or absence of a condensing agent such as carbodiimidazole for conversion into the compound wherein D is -CO<sub>2</sub>R' or its salt. The compound wherein D is -CO<sub>2</sub>H or its salt may also be reacted with thionyl chloride or the like for conversion into a compound wherein D is -COCl, and the compound may be then reacted with R'-OH for conversion into the compound wherein D is -CO<sub>2</sub>R' or its salt.

3-2) Production of the compound wherein D is -CO-NR'R'' (wherein NR'R'' is as defined above) or its salt

**[0191]** The compound wherein D is -CO<sub>2</sub>H or its salt synthesized in 1-5) may be reacted with NHR'R'' (as defined above) in a solvent which is not involved in the reaction in the presence or absence of a condensing agent such as carbodiimidazole for conversion into the compound wherein D is -CO-NR'R'' or its salt. The resulting compound wherein D is -CO-NR'R'' or its salt may be reacted with a reducing agent such as lithium aluminum hydride or diisobutylaluminum hydride to convert the compound into the compound wherein D is -CHO or its salt. The resulting compound wherein D is -CO-NR'R'' or its salt may be also reacted with a reducing agent such as lithium aluminum hydride or diisobutylaluminum hydride to convert the compound into the compound wherein D is -CH<sub>2</sub>-NR'R'' or its salt.

3-3) Production of the compound wherein D is -CO-R or its salt

**[0192]** The compound wherein D is -CO<sub>2</sub>H or its salt synthesized in 1-5) may be reacted with a nucleophilic reagent such as methyllithium or phenyllithium in a solvent which is not involved in the reaction for conversion into the compound wherein D is -CO-R or its salt. The reaction with the nucleophilic reagent may be accomplished by using the compound wherein D is -CO<sub>2</sub>R' or its salt obtained in 3-1) or the compound wherein D is -CO-NR'R'' or its salt obtained in 3-2).

**[0193]** Next, typical conversion process of the substituents A-B and T-Q are described.

**[0194]** It should be noted that most of the production processes are included in the production processes as described above for the conversion of the substituent D.

**[0195]** For example, when the substituent B or T is carbonyl group, the substituent may be derived by reaction with A-CO-W or Q-CO-W in accordance with the procedure described in 1-2) in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid. Alternatively, the substituent may be derived by condensation using A-CO<sub>2</sub>H or Q-CO<sub>2</sub>H as described in 3-2).

**[0196]** When the substituent B or T is -S(O)<sub>z</sub>-, the substituent may be derived by reaction with A-S(O)<sub>z</sub>-W or Q-S(O)<sub>z</sub>-W in accordance with the procedure described in 1-2) in a solvent which is not involved in the reaction in the presence or absence of a base or in the presence or absence of an acid.

**[0197]** When the substituent B or T is an optionally substituted C<sub>1-2</sub> alkylene group, the substituent may be derived by converting the hydroxyl moiety of the corresponding alcohol form into a leaving group followed by nucleophilic substitution in accordance with the procedure described in 1-3); by using reductive amination of the corresponding aldehyde forms shown in 2-3); or by reducing the bond formed through the carbonyl as described above.

**[0198]** When the substituent B is single bond, the substituent may be derived by using A-W through coupling reaction using the metal as described in 1-3); or by reacting the compound with an organic base such as triethylamine or diisopropylethylamine or an inorganic base such as potassium carbonate or sodium hydroxide in a polar solvent such as DMF, 2-ethoxyethanol, ethanol, or water at solvent reflux temperature or by heating in a sealed tube.

**[0199]** It should be noted that, when the compound synthesized by <Production process 1>, <Production process

2>, <Production process 3> or <Production process 4> has a reactive group such as hydroxyl group, amino group, carboxyl group, or thiol group as its substituent, such group may be protected with a protective group as desired in each reaction step and the protective group may be removed at an adequate stage. The process of such introduction/removal of the protective group may be adequately determined depending on the group to be protected and the type of the protective group, for example, by the process described in review section of "Protective Groups in Organic Synthesis", Second edition, 1991, John Wiley & Sons, Inc.

[0200] Furthermore, geometric isomer, tautomer, optical isomer and other stereoisomers may be present for the compound of the present invention when X is methine carbon or when substituent D is present. These isomers and mixtures thereof are within the scope of the present invention. Isolation or purification of such stereoisomer may be accomplished by any of the techniques commonly used in the art, for example, recrystallization and various chromatographic processes. It is also possible to separately produce such isomer by asymmetric synthesis.

<Pharmacophore of the present invention and its practical use>

[0201] The pharmacophore of the present invention is the one which has been described in the seventeenth aspect of the present invention, and more specifically, the one described in detail in [17-a] to [17-e]. The use of such pharmacophore enables designing and/or screening of an inhibitor which selectively inhibits FXa by reversibly binding to the active site of the FXa to develop competitive inhibitory activity for the FXa. In particular, when the information of the pharmacophore of the present invention is provided to a computer system, a rapid evaluation of a large number of compounds will be enabled, and such evaluation will greatly increase the efficiency of the biological tests which require enormous expenditure and time. Such evaluation will also enable to limit the number of compounds actually synthesized and greatly increase the efficiency of the synthetic process.

[0202] Two factors should be considered in the designing and/or screening of the compound which binds to the active site of the FXa to inhibit the FXa. First, the compound should be capable of physically/structurally binding to the active site of the FXa. The noncovalent bond between a protein and an inhibitor generally takes the form of electrostatic interaction, hydrogen bond, van der Waals interaction, or hydrophobic interaction. Second, the compound should be capable of taking the conformation which enables the compound to bind to the active site of the FXa. An efficient designing and/or screening of the inhibitor is enabled by selecting the compound which meets such conditions and the pharmacophore of the present invention.

[0203] The discovery of the FXa inhibitory compound which fulfills the factors as described above may be accomplished by utilizing information on the three-dimensional structure of the FXa in combination with various computer programs and databases. A compound which exhibits FXa inhibitory activity can be detected by selecting the compounds which satisfy the pharmacophore of the present invention by the method as described below; purchasing or synthesizing the compound; and evaluating the compounds for their FXa inhibitory activity by a standard method.

Method 1)

[0204] Low molecular weight compounds are docked in the active site of the FXa. The three-dimensional structure of the FXa is disclosed by PDB, and the structure of the active site is available from PDB. The docking may be accomplished by various computer programs. Use of the computer database of the three-dimensional compounds enables a screening from several million to several ten millions of compounds as well as screening of the non-existing compounds. After selecting the compounds exhibiting the shape complementary to the active site of the FXa, the compounds exhibiting a binding mode which satisfy the pharmacophore of the present invention are extracted. The binding mode can be confirmed by using various molecular graphics software programs.

Method 2)

[0205] Compounds having both hydrophobic moiety and basic moiety are first selected from the database, and it is also possible to preliminarily include the non-existing compounds in the database. Three-dimensional structure of the selected compounds of low molecular weight are then docked in the active site of the FXa, and the compounds exhibiting a binding mode which satisfy the pharmacophore of the present invention are extracted. The docking may be accomplished by various computer programs, and the binding mode can be confirmed by using various molecular graphics software programs.

Method 3)

[0206] Low molecular weight compounds are docked to each of the S1 pocket and the S3 pocket of the FXa, respectively, so that the pharmacophore of the present invention is satisfied. The compounds used may be those of the



computer database of three-dimensional compounds or any compounds or their fragments. The compound which was placed to the S1 pocket and the compound which was placed to the S3 pocket were connected by using an adequate skeleton which does not change relative spatial position. This process can also be accomplished by using various computer programs.

#### Method 4)

**[0207]** Complex structures between a chymotrypsin-like serine protease and its substrate or the inhibitor are prepared. The three-dimensional structure of the protease and the three-dimensional structure of the FXa are overlaid on each other at the structure-conserved area of the chymotrypsin-like serine protease family to thereby construct a virtual docking model between the substrate or the inhibitor and the FXa. The structure of the substrate or the inhibitor is then altered to satisfy the pharmacophore of the present invention. This process can also be accomplished by using various computer programs.

**[0208]** The designing and/or screening of the compounds as described above may be accomplished by using the so called molecular design-assisting integrated computer system such as Insight II, Cerius2, Sybyl, and their modules. Insight II and Cerius2 are available from Molecular Simulations Inc., San Diego, CA, USA, and Sybyl is available from Tripos Inc., St. Louis, MO, USA. In addition to these programs, computer programs with specialized functions are also useful in the processes of detecting the low molecular weight compounds which fit with the structure of the active site; detecting the adequate compounds which satisfies the pharmacophore; or docking the low molecular weight compounds to the structure of the active site. Exemplary such programs include those as described below.

- DOCK [I.D.Kuntz et al., "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161: 269-288 (1982)]. DOCK is commercially available from University of California, San Francisco, CA, USA.
- Catalyst [Green, J. et al., "Chemical Function Queries for 3D Database Search", J. Chem. Inf. Comput. Sci. 34, 1297-1308 (1994)]. Catalyst is commercially available from Molecular Simulations Inc., San Diego, CA, USA.
- Ludi [Bohm, H. J. "LUDI: rule-based automatic design of new substituents for enzyme inhibitor or leads", J. Comput. Aided Mol. Des., 6: 593-606 (1992)]. Ludi is commercially available from Molecular Simulations Inc. San Diego, CA, USA.
- C2-LigandFit. C2-LigandFit is commercially available from Molecular Simulations Inc., San Diego, CA, USA.
- FlexX [Rarey, M. et al., "A fast flexible docking method using an incremental construction algorithm", J. Mol. Biol., 261: 470-489 (1996)]. FlexX is commercially available from Tripos Inc., St. Louis, MO, USA.

**[0209]** The compound having FXa inhibitory activity may also be designed or searched by a process other than the compound designing/screening process described in the present invention or the computer systems.

**[0210]** As shown in the tenth to eighteenth aspects of the present invention as typical use of the pharmacophore of the present invention,

an inhibitor which competitively binds to the active site of the FXa or its fragment may be identified by:

providing three-dimensional structural information of the active site of the FXa (available by the method as described below) to a computer system;

identifying a compound which is assumed to bind to the FXa in a manner satisfying the pharmacophore of the present invention, namely, all of the conditions that:

- (a) the compound associates with S1 pocket [the definition of the S1 pocket is the same as that defined in the tenth or seventeenth aspect] by its hydrophobic moiety, and the compound interacts with Tyr228,
- (b) the compounds associates with S3 pocket [the definition of the S3 pocket is the same as that defined in the tenth or seventeenth aspect] of the active site by its basic moiety, and
- (c) the compound does not form covalent bond with Ser195; and

subjecting the compound to a biological assay which is capable of measuring FXa inhibitory activity to thereby determine whether the compound exhibits FXa inhibitory activity in the assay and identify the desired FXa inhibitor.

**[0211]** To be more specific, the inhibitor may be identified by providing a computer system with the three-dimensional structural information of the FXa molecule containing the active site defined by coordinates of Table A as described below; depicting the three-dimensional structure of the active site in the computer system; overlaying the three-dimensional structure of a test compound on the three-dimensional structure of the active site such that the three-dimensional structure of the test compound is arranged to meet all of the following conditions that:

- (a) the hydrophobic moiety is arranged in the S1 pocket so that the hydrophobic moiety can interact with the Tyr228;

(b) the basic moiety is arranged in the S3 pocket; and  
 (c) no covalent bond is formed with the Ser195; evaluating whether the three-dimensional structure of the test compound spatially fits with the active site; preparing the test compound which spatially fits with the active site; and subjecting the test compound to a biological assay which is capable of measuring FXa inhibitory activity to thereby determine whether the test compound exhibits FXa inhibitory activity in the assay and identify the desired FXa inhibitor.

**[0212]** Alternatively, drug design may be accomplished by conducting an evaluation on a computer by using the three-dimensional structural information of the FXa or its fragment for a compound which satisfies the following association conditions:

- (a) the compound associates with the S1 pocket by its hydrophobic moiety, and the compound interacts with the Tyr228;
- (b) the compound associates with the S3 pocket by its basic moiety; and
- (c) the compound does not form covalent bond with Ser195.

**[0213]** Furthermore, a more specific identification or molecular designing of the FXa inhibitor is enabled by adding the condition for the pharmacophore of the present invention that interaction with the Tyr228 is mediated by the halogen atom, methyl group, or ethyl group (preferably chlorine atom or bromine atom) constituting a part of the hydrophobic moiety.

**[0214]** Alternatively, the identification or molecular designing of the FXa inhibitor may be accomplished by adding the condition that, in the interaction with the Tyr228, the centroid of the hydrophobic moiety and the centroid of the Tyr228 side chain is within the range of 6.9 to 7.9 Å.

**[0215]** Alternatively, the identification or molecular designing of the FXa inhibitory compound may be accomplished by adding the condition that the pharmacophore also satisfies at least one of the following conditions 1) to 3):

1) when the compound binds to the FXa, the hydrophobic moiety does not either partly or entirely undergo an electrostatic interaction with the Asp189 of the S1 pocket;

2) when the compound binds to the FXa, centroid position of the hydrophobic moiety satisfies in the S1 pocket at least two of the following conditions that such position is:

- i) at a distance of 3.6 to 4.6 Å from the Cys191 backbone C<sub>α</sub> atom;
- ii) at a distance of 6.2 to 7.2 Å from the Ser195 backbone C<sub>α</sub> atom;
- iii) at a distance of 5.5 to 6.5 Å from the Ser214 backbone C<sub>α</sub> atom;
- iv) at a distance of 3.6 to 4.6 Å from the Trp215 backbone C<sub>α</sub> atom;
- v) at a distance of 6.7 to 7.7 Å from the Glu217 backbone C<sub>α</sub> atom; and
- vi) at a distance of 5.8 to 6.8 Å from the Cys220 backbone C<sub>α</sub> atom; and

3) when the compound binds to the FXa, centroid position of the partial structure including the basic moiety of the La satisfies in the S3 pocket at least two of the following conditions that such position is:

- i) at a distance of 4.1 to 5.5 Å from the Tyr99 side chain centroid;
- ii) at a distance of 3.1 to 4.5 Å from the Phe174 side chain centroid;
- iii) at a distance of 4.1 to 5.5 Å from the Trp215 side chain centroid;
- iv) at a distance of 4.1 to 6.3 Å from the Lys96 backbone carbonyl oxygen atom; and
- v) at a distance of 3.5 to 5.1 Å from the Glu97 backbone carbonyl oxygen atom.

**[0216]** Alternatively, the identification or molecular designing of the FXa inhibitor may be accomplished by adding the condition that all of the conditions 1) to 3) are satisfied.

**[0217]** Furthermore, the molecular designing of the FXa inhibitor may be accomplished by adding the means for suppressing alteration of the conformation of the cross-linking group described in the aspect [18-e].

**[0218]** The thus identified or designed compound may be obtained by purchasing or synthesizing the compound, and the compound may be subjected to the bioassay, for example, the one described in the Examples of the present invention to determine its specific pharmacological activities, for example, in vitro IC<sub>50</sub>.

**[0219]** With regard to the compound of the present invention, the compound is the one having a FXa inhibitory activity of up to 1 μM in terms of IC<sub>50</sub>, and preferably, the one which was unknown at the time of the filing of the present invention.

**[0220]** The present invention is also directed to a pharmaceutical composition characterized by its inclusion as an effective component of at least one compound which has been identified or designed by the identification or drug

designing method as described above, which has FXa inhibitory activity in terms of  $IC_{50}$  determined by a bioassay of up to 1  $\mu M$ , and which was (1) unknown at the time of the filing of the present invention or (2) known but whose biological activity was unknown at the time of the filing of the present invention. Usefulness of such pharmaceutical composition will be appreciated by referring to the second aspect of the invention or detailed description for the composition containing the compound of the present invention as described below.

**[0221]** The present invention is also directed to a FXa inhibitor characterized by its inclusion as an effective component of at least one compound which has FXa inhibitory activity in terms of  $IC_{50}$  determined by a bioassay of up to 1  $\mu M$ , and which was (1) unknown at the time of the filing of the present invention or (2) known but whose biological activity was unknown at the time of the filing of the present invention. Usefulness of such FXa inhibitor will be appreciated by referring to the third aspect of the invention or detailed description for the composition containing the compound of the present invention as described below.

**[0222]** It should be noted that, of the thus identified or designed compounds of the present invention, the preferred is the one having the FXa inhibitory activity in terms of  $IC_{50}$  of up to 0.5  $\mu M$ , more preferably up to 0.1  $\mu M$ , and most preferably up to 0.01  $\mu M$ .

**[0223]** It should be noted that the identification or designing of such compound may be accomplished by assuming that the compound has a partial structure comprising the spiro skeleton which is the structure wherein one or both of La and Lb have been removed from the general formula (I'), and then defining the residual Lb, the residual La, or the residual Lb and La.

**[0224]** In such procedure, Lb may be defined, for example, after assuming the group represented by A-B- of formula (I) as a particular La, and for example, after setting the condition of the aspect 10-d, 4), namely the condition that "La has an optionally substituted, five- to six-membered, aromatic monocyclic heterocyclic group" for the La, and in particular, after assuming that La comprises 4-pyridyl group. Alternatively, La may be defined by assuming the group represented by -T-Q of formula (I) as a particular Lb, and preferably, by assuming that Lb comprises a group wherein Q is the one described in the aspect [1-1-d] and T is the one described in the aspect [1-8-b], and most preferably, p-halogenostylylsulfonyl group, 6-halogenonaphthalen-2-ylsulfonyl group, or 7-halogeno-2H-benzopyran-3-ylsulfonyl group, as will be understood from the foregoing description.

**[0225]** Next, the therapeutic/prophylactic agent and the pharmaceutical composition of the present invention is described. The pharmaceutical composition of the present invention should contain at least one compound represented by formula (I) or formula (I'), formula (V), formula (VI), formula (Ik), formula (I-a'), formula (I'), or formula (I'') (the definition which may be as defined above) as its effective component, and the composition may also contain a pharmacologically acceptable carrier. The preferable compounds for the compound represented by formula (I) are the same as those described above.

**[0226]** FXa inhibitory action of the compounds of the present invention

**[0227]** The compounds of the present invention possess a potent FXa inhibitory activity. In other words, the compositions of the present invention are a potent FXa inhibitor, and more particularly, a specific FXa inhibitor, which does not inhibit other enzymes.

**[0228]** The compositions of the present invention are also an orally administrable FXa inhibitor, and more specifically, an orally administrable specific FXa inhibitor. The compounds of the present invention specifically inhibit activity of the FXa among the many serine proteases. To be more specific, it does not inhibit trypsin or chymotrypsin at all, nor do they inhibit thrombin, which is another serine protease in the blood coagulation cascade. Hence, the compounds of the present invention solve the aforementioned problems associated with the use of the conventional thrombin inhibitors, for example, the tendency to cause bleeding. As further advantage, the compounds of the present invention can be rapidly absorbed by the digestive tract after oral administration with no reduction in its activity by the absorption, and it also exhibit favorable absorption, distribution, metabolism, and excretion characteristics. Its value as an orally administrable agent is quite high.

**[0229]** The compositions containing the compounds of the present invention can be used as preventives and/or therapeutics of diseases wherein an FXa inhibitor is useful.

**[0230]** The compositions containing the compounds of the present invention can also be used as an anticoagulant, and as preventives and/or therapeutics of diseases for which anticoagulant is useful.

**[0231]** To be more specific, such agents are effective in prevention and/or treatment of diseases caused by thrombus or embolism. To mention specific examples of such diseases, they include: diseases from ischemic cerebrovascular disorders such as cerebral thrombosis, brain infarction, cerebral embolism, transient cerebral ischemic attack (TIA) and cerebral vascular spasm after subarachnoid hemorrhage; Alzheimer's disease, cerebrovascular dementia, asymptomatic cerebrovascular disorder, disease associated with ischemic heart disease such as acute and chronic myocardial infarction, aftereffect after myocardial infarction, unstable angina pectoris, angina pectoris and coronary thrombolysis; thrombogenesis after artificial blood vessel or artificial valve replacement, reocclusion and restenosis after coronary artery bypass grafting, reocclusion and restenosis after PTCA or PTCA or stent placement, pulmonary infarction, lung thrombus/lung embolism, diseases associated with pulmonary vascular disorder (for example, drug-induced pneu-

monia), acute respiratory distress syndrome (ARDS), acute nephritis, acute progressive nephritis, chronic nephritis (for example, diabetic nephropathy, chronic glomerulonephritis, and IgA nephropathy), acute arterial occlusive disease, thromboangitis obliterans (Buerger disease), arteriosclerosis obliterans, peripheral arterial occlusive disease, peripheral venous occlusive disease, deep vein thrombosis, thrombophlebitis, disseminated intravascular coagulation (DIC), organ failures induced with the progress of the shock or DIC, thrombotic microangiopathy (TMA), systemic inflammatory response syndrome (SIRS), thrombotic thrombocytopenic purpura, hemolytic uremic syndrome (HUS), diseases associated with various vascular disorders such as thrombogenesis in extracorporeal circulation, thrombocytopenia in major operation, arterial sclerosis, cancer metastasis, rejection in transplantation, and organ protection or functional improvement in transplantation. Also included are prophylaxis of vascular endothelial cell injury associated with diabetes, hypercoagulation associated with transplantation or activated protein C (APC) resistance, blood hypercoagulation associated with vascular disease, injury after operation, obesity, pregnancy, use of oral contraceptive, sustained depression, heparin induced thrombocytopenia, collagen disease (for example, antiphospholipid syndrome, polyarteritis, and systemic lupus erythematosus), Bechet's disease, ischemic reperfusion injury, cancer or the like, and toxemia in pregnancy.

**[0232]** The agents of the present invention are particularly adapted for use in prevention of embolism associated with atrial fibrillation/artificial valve or valvular heart disease, and preferably for prevention of onset of cerebral embolism, prevention of transient cerebral ischemic attack and especially for prevention of recurrence of the transient cerebral ischemic attack, and prevention/treatment of deep vein thrombosis or DIC.

**[0233]** When the agents of the present invention are used as a drug for these diseases, preventive administration is recommended and such use is particularly important since the agents of the present invention are neither a direct thrombolytic agent nor a direct anti-platelet agents. In other words, the agents of the present invention are adapted for preventive use in patients suffering from thrombophilia or patients having the risk factor of thrombus/embolism for the purpose of preventing thrombus/embolism. In the case of the patients with atrial fibrillation/artificial valve or valvular heart disease, thrombosis is easily generated at the site of the lesion or the transplantation, and such thrombosis often triggers cerebral infarction, which is more than often a fatal attack. The agents of the present invention have a good potential to be a potent drug for preventing onset of the thrombus/embolism, and in particular, cerebral embolism induced in such patients.

**[0234]** Such therapy is continued for a long time. The agents of the present invention can be administered by oral administration with less side effects such as bleeding, and therefore, the agents of the present invention can be reliably used for a long time with no need of frequent monitoring.

**[0235]** In other words, the agents of the present invention are preventives and/or therapeutics for embolism associated with atrial fibrillation/artificial valve or valvular heart disease. Also, the agents of the present invention are preferably preventives of the onset of cerebral embolism associated with such disease. The agents of the present invention are also preventives and/or therapeutics, and in particular, a preventives of the onset of transient cerebral ischemic attack; and a preventives and/or therapeutics for deep vein thrombosis or DIC.

**[0236]** In addition, some compounds of the present invention are easily metabolized in the course of the absorption and secretion of the pharmaceutical substance by the substituent in D, and some of the thus produced metabolites are within the scope of the compound of the present invention as represented by formula (I), and exhibit a potent inhibitory activity for FXa. This is a finding quite interesting in pharmacological/pharmacokinetical point of view.

**[0237]** The compositions containing the compounds of the present invention as an active ingredient are also effective as veterinary drugs and have high value of use. The compositions are also useful as a reagent adapted for use in measuring various blood coagulative functions and as a laboratory reagents.

**[0238]** Owing to the FXa inhibitory action of the compounds of the present invention, such compositions are also useful as preventives/therapeutics for infection by influenza virus based on the inhibitory activity for the propagation of the influenza virus, and also, as preventives/therapeutics for periodontal disease.

**[0239]** Next, the present invention is further described by referring to Experimental Examples and Examples which by no means limit the scope of the present invention.

**[0240]** Excellent FXa inhibitory activity of the compounds of the present invention is confirmed by the test as described below.

1) Measurement of enzyme inhibitory action

a) Measurement of human FXa inhibitory action

**[0241]** In vitro FXa inhibitory activity is measured in accordance with the method of Kettner et al. (Journal of Biological Chemistry, vol. 265, pages 18289 to 18297, 1990). To be more specific, human FXa (product of Enzyme Research Laboratories, Inc., 0.019 U/ml) is mixed with a test compound diluted with dimethylsulfoxide (DMSO) at various concentrations and a synthetic substrate S-2222 (Chromogenix AB, 0.4 mM). The mixtures are incubated at 37°C in Tris-

hydrochloric acid buffer (pH 7.5) while the absorbance at 405 nm is measured continuously. To calculate the FXa inhibitory activity of the test compound, the initial reaction velocity is compared with the value for a control containing no test compound. It should be noted that the FXa inhibitory activity of the test compound is generally indicated as IC<sub>50</sub>.  
**[0242]** When the compounds of the present invention are evaluated for its FXa inhibitory activity by the procedure as describe above, the strength is in the range of 0.1 nM to 1  $\mu$ M in terms of IC<sub>50</sub>. Table 1 shows typical measurements.

Table 1

Test compound (compounds of the Examples)	IC <sub>50</sub> ( $\mu$ M)
Example 1	0.0032
Example 5	0.0029
Example 10	0.0054
Example 25	0.0015
Example 50	0.0019
Example 59	0.0034
Example 61	0.0028

## 2) Measurement of anticoagulant activity (in vitro)

### Measurement of intrinsic coagulation time

**[0243]** Activated partial thromboplastin time (APTT) is measured in the presence of the test compounds diluted at various concentrations. A test compound diluted with DMSO at various concentrations is mixed with human plasma and APTT reagent. The mixture is incubated at 37°C for 2 minutes; calcium chloride (25 mM) is added to the mixture; and the coagulation time is thereafter measured. It should be noted that the anticoagulant activity of the test compound is described in terms of the concentration required to double the coagulation time for the case where no test compound is added. In this test, the compounds of the present invention were found to be effective in extending the APTT. The effects of the compounds of the present invention are shown in Table 2.

Table 2

Test compound (compounds of the Examples)	Concentration required to double coagulation time ( $\mu$ M)
Example 5	0.43
Example 6	0.99
Example 9	0.29
Example 23	0.62
Example 29	0.90
Example 42	0.20
Example 58	0.18
Example 69	0.36

## 3) Characteristics of anticoagulant activity (ex vivo)

### a) Ex vivo measurement of coagulation time in rats (i.v.)

**[0244]** Male Wistar rats (200 g - 300 g; Japan SLC Inc.) that have been starved for more than 12 hours are administered through a femoral vein with a single dose of a drug (3 - 30 mg/kg) dissolved in physiological saline (or 10% DMSO solution), and the blood is collected at a certain time interval (3.8% sodium citrate, 1/10 volume), and plasma is then separated by centrifugation at 3000 rpm for 10 minutes. Prothrombin time (PT) is measured by the procedure as described below by using the separated plasma.

**[0245]** 50  $\mu$ l of the plasma is incubated at 37°C for 3 minutes and 100  $\mu$ l of thromboplastin solution is added to start coagulation. The coagulation time is measured. In the actual test, the intravenously administered compounds of the present invention were found to be effective in extending the PT on account of enzyme inhibition.

### b) Ex vivo measurement of coagulation time in rats (p.o.)

**[0246]** The test compound is compulsorily administered by oral administration using an oral introducer instead of the

administration from the femoral vein at a single dose in the test a), and a certain volume of the blood is collected at a certain time interval at 3.8% sodium citrate, 1/10 volume. The blood is evaluated by the procedure as described in a) for extrinsic coagulation time and intrinsic coagulation time.

**[0247]** In this test b), the compounds of the present invention were found to be effective in extending the coagulation time upon oral administration of 10 - 100 mg.

**[0248]** It should be noted that no abnormality in the aspect of safety is observed in the ex vivo test of the rat.

**[0249]** The pharmaceutical compositions of the present invention may contain at least one compound represented by formula (I) (as already defined above) or salts thereof as an active ingredient. They may also contain any pharmaceutical acceptable carriers. The preferred examples of the compounds of the general formula (I) have already been mentioned.

**[0250]** As described above, the compounds of the present invention exhibit potent inhibitory action for FXa activity without exhibiting any inhibitory activity for trypsin, chymotrypsin, or thrombin, and the specificity of the compounds is high. Furthermore, the compounds of the present invention exhibit antithrombotic action when orally administered at a dose of 0.1 to 10 mg/kg, or intravenously administered at a dose of 0.01 to 1 mg/kg in rats.

**[0251]** On the other hand, the compounds of the present invention does not exhibit prolongation of bleeding time when orally administered at a dose of 10 mg/kg or intravenously administered at a dose of 1 mg/kg in rats. Accordingly, the compounds of the present invention exhibit the anticoagulation action with no risk of showing bleeding tendency, and this is a significant difference from heparin and warfarin, which are known anticoagulants. In addition, the compounds of the present invention exhibit excellent oral absorption, adequate long-lasting action, as well as high safety.

**[0252]** The compounds of the present invention may be administered to the disease as described above which is to be prevented and treated by the present invention either alone or in combined application with other pharmacologically active component. Exemplary such pharmacologically active components include known fibrinolytics (for example, tissue plasminogen activators (tPA) and their derivatives (including modified agents or the so called "second generation" agents), urokinase, and streptokinase); known anticoagulants (for example, warfarin, heparin, and thrombomodulin); known inhibitors of platelet aggregation (for example, aspirin, thromboxane antagonist, inhibitor of thromboxane synthesis, and GPIIb/IIIa antagonist); known therapeutic agents for hyperlipidemia (for example, clofibrate and related drugs, HMG-CoA reductase inhibitor, and EPA-E); and known hypotensive agents (for example, nifedipine and diltiazem).

**[0253]** The term "combined application" as used herein covers not only the administration of a combination drug containing both the compound of the present invention and another pharmacologically active ingredient but also the case where the two are in separate dosage forms and administered either at a time or at different times. The mode of administration is in no way limited as long as the compound of the present invention and another pharmacologically active ingredient exist simultaneously in the patient's blood.

**[0254]** The pharmaceutical composition containing one or more compounds of the present invention or its pharmaceutically acceptable salt as its effective component may be prepared into capsules, pills, tablets, granules, subtle granules, or powder; or alternatively, oral solution such as suspension, emulsion, limonades, elixir, or syrup; injectable solution; transnasal formulation; suppository; ointment; epithem; and the like which are orally or perorally administered to human and other animals by using the commonly used pharmaceutical vehicle, excipient, or other additives.

**[0255]** Clinical dose of the compound of the present invention to human may be adequately determined in consideration of symptom, body weight, age, sex, and the like of the patient to which the compound is administered. The adult daily dose in oral administration is generally in the range of 0.1 mg to 1000 mg, and preferably 1 mg to 300 mg, and the dose in peroral administration is 0.01 to 300 mg, and preferably 0.1 mg to 100 mg. Such dose may be administered as a single dose or divided into several doses. The dose may vary depending on various conditions, and the dose below the above described range may be sufficient in some cases.

**[0256]** In order to accomplish oral administration according to the present invention, capsules, pills, tablets, powder, granules, and the like may be employed for the solid composition. Such solid composition is produced by combining at least one active substance with at least one inactive carrier. To be more specific, the composition may contain an excipient (for example, lactose, saccharose, mannitol, glucose, hydroxy propylcellulose, microcrystalline cellulose, or metasilicic acid), a binder (for example, crystalline cellulose, saccharide, dextrin, hydroxy propylcellulose, hydroxy propylmethylcellulose, polyvinyl pyrrolidone, or Macrogol), a lubricant (for example, magnesium stearate, calcium stearate, or talc), a disintegrant (for example, corn starch, carboxy methyl cellulose, or calcium cellulose glycorate), a stabilizer (for example, lactose and other sugar alcohols or sugar), a solubilizer or a solubilizing aid (for example, cholesterol, triethanolamine, glutamic acid, or aspartic acid), a colorant, a flavoring agent, an antiseptic, an isotonic agent, a dispersant, an antioxidant (for example, ascorbic acid, or butylhydroxyanisole), a buffer, or a preservative (for example, paraben or benzylalcohol).

**[0257]** It should be noted that the tablet, the pill and the granules may be coated with sugar, gelatin, hydroxy propylmethylcellulose phthalate or other gastric or enteric film coating.

**[0258]** Exemplary injectable solution used for parenteral administration include aseptic aqueous or nonaqueous so-

lution, suspension, and emulsion. Exemplary carriers for the aqueous solution and suspension include water for injection and physiological saline, and exemplary carriers for the nonaqueous solution and suspension include propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and alcohols such as ethylalcohol, and polysorbate 80 (TM).

**[0259]** Such composition may further comprise an isotonic agent, antiseptic, emolient, emulsifier, dispersant, stabilizer, solubilizer, solubilizing aid, or other additives as described above, and these additives may be sterilized, for example, by filtration with a membrane filter, inclusion of an antimicrobial agent, or UV irradiation.

**[0260]** The composition may be also produced in the form of sterilized solid composition which can be dissolved, emulsified, or suspended before its use for use as an injectable solution. When the compound of the present invention has low solubility, the compound may be solubilized as desired.

**[0261]** Such solubilization may be accomplished by any of the processes known in the art to be applicable for the production of drugs, for example, addition of a surfactant (a polyoxyethylene hydrogenated castor oil, a polyoxyethylene sorbitan higher fatty acid ester, a sugar fatty acid ester, and the like); and formation of a solid dispersion of the drug and a solubilizer, for example, a polymer (a water-soluble polymer such as polyethylene glycol (PEG), hydroxy propyl methylcellulose (HPMC), or polyvinyl pyrrolidone (PVP); or an enteric polymer such as hydroxy propyl methylcellulose phthalate (HPMCP), or methyl methacrylate-methacrylic acid copolymer (Eudragid L,S (TM) manufactured by Rohm and Haas Company)). If desired, an inclusion compound may be formed by using  $\alpha$ -,  $\beta$ -, or  $\gamma$ -cyclodextrin, hydroxy propyl cyclodextrin, or the like. The procedure employed for the solubilization may also be modified as desired depending on the drug desired by referring to Nagai, T., et al., "Monograph in Pharmacology No.1, Biochemical Availability", Soft-Science Inc., 78-82(1988) or Utsumi, I., et al., "Current Pharmaceutical Technology and Its Application", Iyaku Journal, 157-159(1983). Among these, the preferred is formation of a solid dispersion comprising the drug and the solubilizer which exhibits an improved solubility (JP-A 56-49314, FR2460667).

#### <Formulation Examples>

**[0262]** Next, examples of the pharmaceutical composition of the present invention are described. The "Compound M" is the compound of the present invention represented by formula (I) or its pharmaceutically acceptable salt, and to be more specific, a compound selected from the compounds described in Examples.

(a) Tablet (1 mg)	
Compound M	1.0 g
Lactose	90.0 g
Sodium carboxymethyl cellulose	7.0 g
Corn starch paste(5% W/V paste)	1.0 g
Magnesium stearate	1.0 g

**[0263]** The ingredients as described above were measured and made into 100 mg tablet by normal procedure.

(b) Tablet (10 mg)	
Compound M	10 g
Lactose	150 g
Crosscarmellose sodium	6.0 g
Corn starch	28.5 g
Polyvinyl pyrrolidone	2.5 g
Magnesium stearate	3 g

**[0264]** The ingredients as described above were measured and made into 200 mg tablet by normal procedure, and the tablet was coated with cellulose acetate phthalate to produce an enteric tablet.

(c) Tablet (100 mg)	
Compound M	100 g
Lactose	180 g
Crosscarmellose sodium	13 g
Corn starch (5% W/V paste)	4 g
Magnesium stearate	3 g

[0265] The ingredients as described above were measured and made into 300 mg tablet by normal procedure.

(d) Capsule (50 mg)	
Compound M	100 g
Lactose	395.5 g
Magnesium stearate	4.5 g

[0266] The ingredients as described above were measured and uniformly mixed. The uniform powder was sealed in a hard capsule (Pharmacopeia No.1) at 250 mg/capsule.

(e) Injectable solution (0.1 mg/ml)	
Compound M	0.1% W/V
Sodium phosphate buffer	2.3% W/V
Citric acid	0.4%
Macrogol 400	3.5%
Water for injection	adequate amount to make up 100%.

[0267] The ingredients as described above were mixed, and the resulting solution was sealed in an injection ample at 1 ml/ample to produce the injectable solution.

(f) Injectable solution (1.0 mg/ml)	
Compound M	1.0% W/V
Sodium phosphate buffer	3.6% W/V
1M Aqueous solution of sodium hydroxide	15% W/V
Water for injection	adequate amount to make up 100%.

[0268] The ingredients as described above were mixed, and the resulting solution was sealed in an injection ample at 1 ml/ample to produce the injectable solution.

#### <Synthesis Examples>

[0269] Next, the present invention is described in further detail by referring to Synthesis Examples which by no means limit the scope of the present invention.

[0270] Nuclear magnetic resonance (NMR) spectrum was measured by using JEOL JNM-EX270 FT-NMR (manufactured by JEOL Ltd.) or JEOL JNM-LA300 FT-NMR (indicated by \* in the data; manufactured by JEOL Ltd.). Infrared absorption spectrum (IR) was measured by using HORIBA FT-200 FT-IR (indicated by \* in the data; manufactured by HORIBA Ltd.) or HORIBA FT-720 FT-IR (manufactured by HORIBA Ltd.). High resolution mass spectrometry (HRMS) spectrum was measured by JEOL JMS-GCMATE (manufactured by JEOL Ltd.). High performance liquid chromatography (HPLC) was conducted by using Shimadzu LC-10A (manufactured by Shimadzu Corporation).

#### (Example 1)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

#### <Step A-1>

Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)amino]acetate

[0271] Glycine ethyl ester hydrochloride (9.88 g) was suspended in methylene chloride (500 ml), and triethylamine (20.2 ml) and then 6-chloronaphthalene-2-sulfonyl chloride (17.6 g) were added to the suspension under cooling with ice. After stirring at room temperature for 1 hour and adjusting the mixture to pH 2 by addition of 1N hydrochloric acid,



the mixture was extracted with methylene chloride. The methylene chloride layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. After washing the resulting crystals in n-hexane, the crystals were collected by filtration and air-dried to obtain the title compound (22.4 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.43-8.40(1H,m), 7.95-7.87(4H,m), 7.57(1H,dd,J=2,9Hz), 5.22-5.15(1H,m), 4.01(2H,q,J=7Hz), 3.82(2H,d,J=6Hz), 1.11(3H,t,J=7Hz)

<Step A-2>

Synthesis of ethyl 2-[(3-acetoxy-2-oxopropan-1-yl) (6-chloronaphthalen-2-ylsulfonyl)amino]acetate

**[0272]** To a solution of the compound obtained in Step A-1 (2.50 g) in N,N-dimethylformamide (25 ml) were added potassium carbonate (1.58 g) and sodium iodide (1.14 g), and a solution of 1-acetoxy-3-chloroacetone (1.72 g) in N,N-dimethylformamide (7 ml) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1.5 hours, and the mixture was extracted with diethyl ether after adding water. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was crystallized in diethyl ether, and the crystals were collected by filtration and air-dried to obtain the title compound (2.72 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.42-8.37(1H,m), 7.98-7.85(3H,m), 7.80(1H,dd,J=2,9Hz), 7.57(1H,dd,J=2,9Hz), 4.84(2H,s), 4.31(2H,s), 4.15(2H,s), 4.06(2H,q,J=7Hz), 2.16(3H,s), 1.17(3H,t,J=7Hz)

<Step A-3>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo [4.3.0] nonane-8,4'-piperidin]-2-one

**[0273]** To a solution of the compound obtained in Step A-2 (1.6 g) and 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine (800 mg) in toluene (200 ml) was added p-toluenesulfonic acid monohydrate (34.0 mg), and the mixture was heated under reflux for 1 hour by using a Dean Stark. The reaction mixture was allowed to cool, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; ethyl acetate) to obtain the title compound (1.08 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36(1H,s), 8.02-7.88(3H,m), 7.78(1H,d,J=9Hz), 7.60(1H,d,J=9Hz), 7.36-7.19(5H,m), 4.48-4.14(5H,m), 3.46(2H,s), 3.34(1H,d,J=17Hz), 3.08(1H,d,J=12Hz), 2.62-2.21(4H,m), 2.33(1H,d,J=12Hz), 2.11(3H,s), 1.93-1.72(2H,m), 1.53-1.34(2H,m)

<Step A-4>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-spiro[bicyclo[4.3.0] nonane-8,4'-piperidin]-2-one

**[0274]** To a solution of the compound obtained in Step A-3 (425 mg) in methanol (11 ml) was added 1N aqueous solution of sodium hydroxide (2.8 ml) under cooling with ice. The reaction mixture was stirred at room temperature for 1 hour, and the solvent was distilled off under reduced pressure. The residue was washed by adding water, collected by filtration, and dried under reduced pressure to obtain the title compound (365 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.40-8.33(1H,m), 8.01-7.90(3H,m), 7.82-7.76(1H,m), 7.65-7.58(1H,m), 7.35-7.21(5H,m), 4.50-4.31(2H,m), 4.24(1H,d,J=12Hz), 3.89(1H,d,J=12Hz), 3.62(1H,d,J=12Hz), 3.47(2H,s), 3.35(1H,d,J=17Hz), 3.07(1H,d,J=12Hz), 2.66-2.07(4H,m), 2.26(1H,d,J=12Hz), 1.97-1.75(2H,m), 1.57-1.36(2H,m)

<Step A-5>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-spiro[bicyclo[4.3.0] nonane-8,4'-piperidin]-2-one

**[0275]** To a solution of the compound obtained in Step A-4 (100 mg), benzyltriethylammonium chloride (4.0 mg), and dimethyl sulfate (0.018 ml) in methylene chloride (2 ml) was gradually added 50% aqueous solution of sodium hydroxide (0.6 ml) with vigorous stirring under cooling with ice. After stirring the reaction mixture at room temperature for 2 hours, water was added under cooling with ice, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was distilled

off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 1:4 - 1:6) to obtain the title compound (48.0 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36-8.33(1H,m), 7.97-7.92(3H,m), 7.80-7.75(1H,m), 7.63-7.57(1H,m), 7.33-7.20(5H,m), 4.40-4.30(2H,m), 4.18(1H,d,J=12Hz), 3.64(1H,d,J=10Hz), 3.54(1H,d,J=10Hz), 3.46(2H,s), 3.41(3H,s), 3.32(1H,d,J=17Hz), 3.10(1H,d,J=12Hz), 2.67-2.18(4H,m), 2.24(1H,d,J=12Hz), 1.99-1.75(2H,m), 1.53-1.33(2H,m)

<Step A-6>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one hydrochloride

**[0276]** To a solution of the compound obtained in Step A-5 (45.0 mg) in 1,2-dichloroethane (2 ml) was added 1-chloroethyl chloroformate (0.021 ml), and the mixture was heated under reflux for 30 minutes. The reaction mixture was allowed to cool, and the solvent was distilled off under reduced pressure. To the residue was added methanol (2 ml), and the mixture was heated under reflux for 30 minutes. The reaction mixture was allowed to cool, and the solvent was distilled off under reduced pressure. The resulting residue was crystallized by adding diethylether, and the supernatant was removed by decantation. The solvent was distilled off under reduced pressure to obtain the title compound (39.5 mg).

NMR spectrum (\*DMSO-d<sub>6</sub>) δppm: 8.89-8.75(1H,brs), 8.73-8.58(1H,brs), 8.61(1H,s), 8.33-8.13(3H,m), 7.93-7.84(1H,m), 7.77-7.69(1H,m), 4.17-4.02(3H,m), 3.57-2.80(7H,m), 3.28(3H,s), 3.18(1H,d,J=12Hz), 2.62(1H,d,J=11Hz), 2.00-1.83(2H,m), 1.70-1.54(2H,m)

<Step A-7>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0277]** To a suspension of the compound obtained in Step A-6 (35.0 mg) and 4-chloropyridine hydrochloride (10.2 mg) in 2-ethoxyethanol (2 ml) was added diisopropylethylamine (0.041 ml), and the mixture was heated under reflux for 2 hours. After allowing the mixture to cool, potassium carbonate (56 mg) was added to the reaction mixture, and the mixture was stirred for 30 minutes. The insoluble content was removed by filtration, and the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 10:1) to obtain the title compound (9.6 mg).

HRMS: C<sub>27</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>5</sub>S(M<sup>+</sup>): Calculated: 556.1547, Found: 556.1540

**[0278]** The resulting compound was optically resolved on HPLC [Waters DeltaPrep 4000 manufactured by Waters Inc.; Column used, Daicel Chiralcel OD manufactured by Daicel Chemical Industries, Ltd., 2 cm x 25 cm; eluent; n-hexane : ethanol : diethylamine = 60:40:1; flow rate, 10 ml/min, detection wavelength, 254 nm] to obtain (+)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one [retention time: 43.5 min, [α]<sub>D</sub><sup>25</sup> +48.8 (c1.247, chloroform), [α]<sub>D</sub><sup>33</sup> +91.3 (c1.000, methanol), >99%ee], and (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one [retention time: 63.0 min, [α]<sub>D</sub><sup>25</sup> -48.4 (c1.175, chloroform), [α]<sub>D</sub><sup>33</sup> -90.7 (c1.000, methanol), >99%ee], respectively.

**[0279]** In addition, racemic body of the title compound (50.9 mg) was mixed with (+)-O,O'-dibenzoyl-D-tartaric acid (32.7 mg), and methanol (6.6 ml) was added to the mixture. After stirring the mixture, the insoluble content was collected by filtration and dried in vacuum. The thus obtained crystals (20 mg) were desalted by using saturated aqueous solution of sodium hydrogencarbonate to obtain the (+) form of the title compound at an optical purity of 94.6%ee. The (-) form of the title compound was also obtained by the similar manner using (-)-O,O'-dibenzoyl-L-tartaric acid.

<Step B-1>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0280]** The compound obtained in <Step A-3> (70.0 g) and 1,8-bis(N,N-dimethylamino)naphthalene (5.00 g) were dissolved in 1,2-dichloroethane (700 ml), and with the solution temperature maintained at 0°C, benzyl chloroformate (33.4 ml) was added dropwise to the solution. The reaction mixture was stirred at room temperature for 2 hours, and saturated aqueous solution of sodium hydrogencarbonate was added under cooling with ice. The mixture was extracted with methylene chloride, and the organic layer was washed with saturated sodium chloride solution and dried over

anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in a mixed solution of methanol (1.33 l) and methylene chloride (1.33 l), and 1N aqueous solution of sodium hydroxide (140 ml) was added dropwise to this solution under cooling with ice. After stirring at room temperature for 30 minutes, the solvent was distilled off under reduced pressure. To the residue was added saturated aqueous solution of ammonium chloride, and the mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 40:1 - 30:1) to obtain the title compound (64.6 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.37-8.33(1H,m), 7.97-7.91(3H,m), 7.80-7.74(1H,m), 7.63-7.58(1H,m), 7.39-7.25(5H,m), 5.10(2H,s), 4.46-4.32(2H,m), 4.22(1H,d, J=12Hz), 3.96-3.85(1H,m), 3.76-3.53(3H,m), 3.52-3.40(1H,m), 3.36(1H,d, J=17Hz), 3.37-3.24(1H,m), 3.15(1H,d, J=12Hz), 2.41(1H,brs), 2.28(1H,d, J=12Hz), 1.89-1.68(2H,m), 1.48-1.34(2H,m)

<Step B-2>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0281]** The procedure of <Step A-5> was repeated by using the compound obtained in Step B-1 (30.0 g) and a large excess of dimethyl sulfate (62.4 ml) to obtain the title compound (26.4 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.34(1H,s), 7.99-7.91(3H,m), 7.80-7.74(1H,m), 7.64-7.58(1H,m), 7.38-7.25(5H,m), 5.09(2H,s), 4.42-4.29(2H,m), 4.16(1H,d, J=11Hz), 3.41(3H,s), 3.65(1H,d, J=10Hz), 3.59(1H,d, J=10Hz), 3.74-3.13(6H,m), 2.25(1H,d, J=12Hz), 1.94-1.66(2H,m), 1.46-1.31(2H,m)

<Step B-3>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0282]** To a solution of the compound obtained in Step B-2 (76.5 g) in acetonitrile (1.53 l) was added trimethylsilyl iodide (32 ml) under cooling with ice. After stirring the mixture for 45 minutes under cooling with ice, the reaction mixture was poured into 1N hydrochloric acid under cooling with ice, and n-hexane was added to this mixture. The mixture was stirred for separation, and the aqueous layer was washed with n-hexane followed by addition of methylene chloride. 2N aqueous solution of sodium hydroxide was added with stirring under cooling with ice and the mixture was adjusted to pH 11. The mixture was extracted with methylene chloride, and the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to thereby obtain the title compound (55.9 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.38-8.32(1H,m), 7.99-7.91(3H,m), 7.82-7.74(1H,m), 7.61(1H,dd, J=2,9Hz), 4.41-4.29(2H,m), 4.21(1H,d, J=12Hz), 3.65(1H,d, J=10Hz), 3.58(1H,d, J=10Hz), 3.41(3H,s), 3.32(1H,d, J=17Hz), 3.20-3.04(2H,m), 3.01-2.74(3H,m), 2.25(1H,d, J=12Hz), 1.98-1.82(2H,m), 1.58-1.38(2H,m)

<Step B-4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0283]** To a solution of the compound obtained in Step B-3 (7.50 g) and 4-chloropyridine hydrochloride (2.34 g) in ethanol (150 ml) was added diisopropylethylamine (13.6 ml), and the mixture was stirred in a sealed tube at 150°C for 15 hours. The reaction mixture was allowed to cool and concentrated. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 100:1 - methanol) to obtain the title compound (1.85 g).

<Step C-1>

Synthesis of ethyl 2-[[[2-(acetoxymethyl)-3,8-diaza-1-oxa-8-benzylspiro[4.5]decan-2-yl]methyl]] (6-chloronaphthalen-2-ylsulfonyl)amino]acetate

**[0284]** To a solution of the compound obtained in Step A-2 (200 mg) and 4-(aminomethyl)-1-benzyl-4-hydroxypipe-

ridine (140 mg) in methylene chloride (7.5 ml) was added 3A molecular sieves (400 mg), and the mixture was stirred at room temperature. 0.09N acetic acid-methylene chloride solution (0.50 ml) was added to this mixture. The mixture was heated under reflux for 3.5 hours, allowed to cool and concentrated, and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 19:1) to obtain the title compound (142 mg).  
 5 NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.37-8.32(1H,m), 7.94-7.76(4H,m), 7.55(1H,dd,J=2,9Hz), 7.33-7.22(5H,m), 4.44(2H,s), 4.14(1H,d,J=12Hz), 4.02(1H,d,J=12Hz), 3.95-3.77(2H,m), 3.60(1H,d,J=15Hz), 3.50(1H,d,J=15Hz), 3.49(2H,s), 3.38-3.23(1H,m), 3.11-2.85(2H,m), 2.62-2.20(4H,m), 2.04(3H,s), 1.82-1.54(4H,m), 1.06(3H,t,J=7Hz)

<Step C-2>

10 Synthesis of 6-(acetoxymethyl)-1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

[0285] A solution of the compound obtained in Step C-1 (125 mg) in toluene was heated under reflux for 2.5 hours. The solution was allowed to cool and concentrated, and the resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 1:8) to obtain the title compound (97.3 mg).

<Step D-1>

20 Synthesis of ethyl 2-(2-hydroxy-3-methoxypropylamino)acetate

[0286] A solution of glycidyl methyl ether (1.00 g) and glycine ethyl ester (5.91 g) in ethanol was stirred overnight, and concentrated under reduced pressure to obtain the title compound (2.17 g).

25 NMR spectrum (\*CDCl<sub>3</sub>) δppm: 4.19(2H,q,J=7Hz), 3.87-3.78(1H,m), 3.39(3H,s), 3.50-3.35(4H,m), 2.81-2.62(2H,m), 1.29(3H,t,J=7Hz)

<Step D-2>

30 Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)(2-hydroxy-3-methoxypropyl)amino]acetate

[0287] To a solution of the compound obtained in Step D-1 (1.60 g) and 6-chloronaphthalene-2-sulfonyl chloride (2.20 g) in methylene chloride (30 ml) was added dropwise triethylamine (1.17 ml) at 0°C. After stirring overnight at room temperature, the reaction mixture was acidified with hydrochloric acid. The mixture was then extracted with ethyl acetate and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 1:1) to obtain the title compound (800 mg).

35 NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38(1H,s), 7.88(1H,d,J=9Hz), 7.87-7.81(3H,m), 7.50(1H,dd,J=2,9Hz), 4.22(2H,s), 4.05(2H,q,J=7Hz), 4.06-3.97(1H,m), 3.33(3H,s), 3.56-3.31(4H,m), 1.14(3H,t,J=7Hz)

40 <Step D-3>

Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)(3-methoxy-2-oxopropyl)amino]acetate

[0288] To a solution of the compound obtained in Step D-2 (220 mg) in methylene chloride (5 ml) was added Dess-Martin reagent (336 mg) at room temperature, and the mixture was stirred overnight. To the reaction mixture was added a 1:1 mixed solution of saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium hydrogensulfate, and after stirring, the mixture was extracted with methylene chloride, and the organic layer was dried over anhydrous sodium sulfate. After distilling off the solvent under reduced pressure, the resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 1:1) to obtain the title compound (190 mg).

50 NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38(1H,s), 7.93-7.77(4H,m), 7.54-7.48(1H,m), 4.44(2H,s), 4.20(2H,s), 4.13(2H,s), 4.02(2H,q,J=7Hz), 3.39(3H,s), 1.13(3H,t, J=7Hz)

<Step D-4>

Ethyl 2-[[[3,8-diaza-2-(methoxymethyl)-1-oxa-8-benzylspiro[4.5]decan-2-yl] methyl] (6-chloro-2-naphthalen-2-ylsulfonyl)amino]acetate

**[0289]** The procedure of Step C-1 was repeated by using the compound obtained in Step D-3 (100 mg) to obtain the title compound (145 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.37-8.32(1H,m), 7.96-7.77(4H,m), 7.56-7.50(1H,m), 7.35-7.22(5H,m), 4.53-4.37(2H,m), 3.93-3.81(2H,m), 3.59-3.54(2H,m), 3.50-3.44(4H,m), 3.34(3H,s), 2.94(1H,d,J=12Hz), 2.86(1H,d,J=12 Hz), 2.68-2.34(4H,m), 1.88-1.53(4H,m), 1.05(3H,t,J=7Hz)

<Step D-5>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0290]** The procedure of Step C-2 was repeated by using the compound obtained in Step D-4 (72.5 mg) to obtain the title compound (67.0 mg).

<Step E>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0291]** The procedure of <Step A-5> was repeated by using the compound obtained in Example 3 <Step A-2> (70 mg) to obtain the title compound (38.7 mg).

<Step F-1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0292]** The procedure of Example 1 <Step A-4> was repeated by using the compound obtained in Example 7 <Step B-1> (938 mg) to obtain the title compound (626 mg).

NMR spectrum (\*CD<sub>3</sub>OD) δppm: 8.52-8.47(1H,m), 8.16-8.04 (3H,m), 7.87(1H,dd,J=2,9Hz), 7.65(1H,dd,J=2,9Hz), 4.32-4.19(2H,m), 4.16(1H,d, J=12Hz), 3.78-3.68(2H,m), 3.48(1H,d,J=17Hz), 3.35-3.25(1H,m), 3.23-3.11(1H,m), 3.08-2.83(3H,m), 2.58(1H,d,J=12Hz), 2.06-1.79(2H,m), 1.66-1.35(2H,m)

<Step F-2>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0293]** The compound obtained in Step F-1 (3.29 g) was suspended in water (132 ml), and after adding sodium carbonate (1.80 g) to the suspension, benzyl chloroformate (1.21 ml) was added dropwise to the suspension with stirring under cooling with ice. The mixture was stirred for 1 hour under cooling with ice and water was added. The mixture was then extracted with methylene chloride and the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 40:1) to obtain the title compound (3.82 g).

(Example 2)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-[2-(methylthio)pyrimidin-4-yl]spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0294]** To a suspension of the compound obtained in Example 1 <Step A-6> (200 mg) and 4-chloro-2-(methylthio)pyrimidine (0.049 ml) in isoamyl alcohol (2 ml) was added sodium hydrogencarbonate (87.5 mg), and the mixture was heated under reflux for 1.5 hours. The reaction mixture was allowed to cool and concentrated, and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain an oily product. This product was solidified in n-hexane, and the solid content was collected by filtration to obtain the title compound (63.2 mg).

NMR spectrum ( $^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.36(1H,s), 8.07-7.90(4H,m), 7.84-7.74(1H,m), 7.67-7.58(1H,m), 6.16(1H,d,J=6Hz), 4.44-4.29(2H,m), 4.24-4.14(1H,m), 3.95-3.28(6H,m), 3.43(3H,s), 3.35(1H,d,J=17Hz), 3.28-3.17 (1H,m), 2.46(3H,s), 2.29(1H,d,J=12Hz), 2.01-1.73(2H,m), 1.53-1.40(2H,m)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0295]** Raney nickel (manufactured by Aldrich Company, 50% aqueous solution, 0.2m 2001) which had been washed with ethanol was added to a solution of the compound obtained in Step 1 (58.0 mg) in ethanol (1 ml), and the mixture was heated under reflux for 1 hour. After allowing the reaction mixture to cool, the catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain the title compound (23.0 mg). HRMS:  $\text{C}_{26}\text{H}_{28}\text{ClN}_5\text{O}_5\text{S}(\text{M}^+)$ : Calculated: 557.1499, Found: 557.1520

(Example 3)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step A-1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one hydrochloride

**[0296]** The procedure of Example 1 <Step A-6> was repeated by using the compound obtained in Example 1 <Step A-3> (584 mg) to obtain the title compound (430 mg).

NMR spectrum ( $^1\text{H}$ ,  $\text{DMSO}-d_6$ )  $\delta$ ppm: 8.77(1H,brs), 8.68-8.52(2H,m), 8.34-8.14(3H,m), 7.93-7.86(1H,m), 7.74(1H,dd, J=2.9Hz), 5.32-5.22(1H,m), 4.17-3.97(3H,m), 3.63-2.80(7H,m), 3.21(1H,d,J=12Hz), 2.63(1H,d,J=12Hz), 2.04-1.84(2H,m), 1.69-1.53(2H,m)

<Step A-2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0297]** The compound obtained in Step A-1 (370 mg) was used to synthesize according to the procedure of Example 1 <Step A-7> to thereby obtain the title compound (30.0 mg).

HRMS:  $\text{C}_{26}\text{H}_{27}\text{ClN}_4\text{O}_5\text{S}(\text{M}^+)$ : Calculated: 542.1390, Found: 542.1421

<Step B >

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0298]** To a solution of the compound obtained in Example 7 <Step A-4> (30.0 mg) in ethanol (1 ml) was added hydrazine monohydrate (0.04 ml), and the mixture was heated under reflux for 30 minutes. The reaction mixture was allowed to cool and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 8:1) to obtain the title compound (20.7 mg).

(Example 4)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step A-1>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0299]** To a solution in methylene chloride (20 ml) of the compound obtained in Example 1 <Step A-4> (1.0 g), benzyltriethylammonium chloride (41 mg) and ethyl bromoacetate (259 ml), was gradually added 50% aqueous solution of sodium hydroxide (6 ml) with vigorous stirring under cooling with ice.

**[0300]** After stirring the reaction mixture for 1.5 hours under cooling with ice, ethyl bromoacetate (120 ml) was added and the mixture was stirred for further 30 minutes. After adding water to the reaction mixture and extracting with methylene chloride, the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain the title compound (413 mg).

NMR spectrum (CDCl<sub>3</sub>) δppm: 8.37-8.32(1H,m), 7.97-7.90(3H,m), 7.80-7.73(1H,m), 7.60(1H,dd,J=2,9Hz), 7.34-7.18(5H,m), 4.42-4.08(7H,m), 3.90-3.73(2H,m), 3.47(2H,s), 3.31(1H,d,J=17Hz), 3.18(1H,d,J=12Hz), 2.68-2.19(4H,m), 2.27(1H,d,J=12Hz), 2.07-1.79(2H,m), 1.66-1.33(2H,m), 1.33-1.22(3H,m)

<Step A-2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one hydrochloride

**[0301]** The compound obtained in Step A-1 (300 mg) was used to synthesize according to the procedure of Example 1 <Step A-6> to thereby obtain the title compound (276 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 9.65-9.45(2H,brs), 8.33(1H,s), 8.00-7.90(3H,m), 7.80-7.73(1H,m), 7.65-7.58(1H,m), 4.40-4.05(7H,m), 3.90(1H,d,J=10Hz), 3.77(1H,d,J=10Hz), 3.42-3.01(6H,m), 2.37-2.09(2H,m), 2.26(1H,d,J=12Hz), 2.05-1.91(1H,m), 1.58-1.45(1H,m), 1.29(3H,t,J=7Hz)

<Step A-3>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0302]** The compound obtained in Step A-2 (200 mg) was used to synthesize according to the procedure of Example 1 <Step A-7> to thereby obtain the title compound (11.4 mg). HRMS: C<sub>30</sub>H<sub>33</sub>ClN<sub>4</sub>O<sub>7</sub> S(M<sup>+</sup>): Calculated: 628.1758, Found: 628.1802

<Step B>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0303]** The compound obtained in Example 3 <Step A-2> (300 mg) was used to synthesize according to the procedure

of Example 4 <Step A-1> to thereby obtain the title compound (168 mg).

(Example 5)

5 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(carboxymethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step A>

10 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(carboxymethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0304]** To a solution of the compound obtained in Example 4 <Step A-3> (10.0 mg) in ethanol (320 ml) was added 2N aqueous solution of potassium hydroxide (32.0 ml) and the mixture was stirred at room temperature for 20 minutes. The reaction mixture was adjusted to pH 5 by adding saturated aqueous solution of ammonium chloride and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 4:1) to obtain the title compound (3.3 mg). IR (\*KBr)cm<sup>-1</sup>: 3412, 3149, 1998, 1744, 1647, 1402

20 <Step B-1>

Synthesis of 1,4-diaza-6-(t-butoxycarbonylmethoxymethyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

25 **[0305]** To a solution in methylene chloride (1.4 ml) of the compound obtained in Example 3 <Step A-2> (85.0 mg), benzyltriethylammonium chloride (3.57 mg) and t-butyl bromoacetate (0.03 ml), was gradually added 50% aqueous solution of sodium hydroxide (0.43 ml) with vigorous stirring under cooling with ice. After stirring the reaction mixture for 40 minutes under cooling with ice, water was added and the reaction mixture was extracted with chloroform. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 20:1 - 15:1) to obtain the title compound (53.5 mg). NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38-8.32(1H,m), 8.28-8.17(2H,m), 8.00-7.89(3H,m), 7.83-7.74(1H,m), 7.66-7.58(1H,m), 6.66-6.56(2H,m), 4.42-4.28(2H,m), 4.19(1H,d,J=11Hz), 4.12(1H,d,J=17Hz), 4.02(1H,d,J=17Hz), 3.96-3.88(1H,m), 3.81-3.72(1H,m), 3.53-3.17(4H,m), 3.35(1H,d,J=17Hz), 3.30(1H,d,J=11Hz), 2.32(1H,d,J=12Hz), 2.16-2.04(1H,m), 1.96-1.82(1H,m), 1.78-1.41(2H,m), 1.50(9H,s)

<Step B-2>

40 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(carboxymethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0306]** The compound obtained in Step B-1 (48 mg) was dissolved in formic acid (1.0 ml) and the solution was stirred overnight at room temperature. The mixture was solidified by addition of diethyl ether and the supernatant was removed by decantation and dried in vacuum to obtain the title compound (35.3 mg).

45 (Example 6)

Synthesis of 1,4-diaza-6-(methoxymethyl)-4-(2-naphthalenesulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

50 **[0307]** To a solution of the compound obtained in Example 1 <Step A-7> (12.0 mg) in methanol (1 ml) was added 10% palladium-active carbon (6.0 mg). The mixture was stirred at room temperature for 3 days under a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; n-hexane : ethyl acetate = 1:1) to obtain the title compound (8.6 mg). HRMS:C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>5</sub> S(M<sup>+</sup>) : Calculated: 522.1937, Found: 522.1949



(Example 7)

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step A-1>

Synthesis of 4-[4-(t-butoxycarbonylamino)methyl-4-hydroxypiperidin-1-yl]pyridine 1-oxide

**[0308]** To a suspension in isoamyl alcohol (35 ml) of conventionally known compounds: 4-[(t-butoxycarbonylamino)methyl]-4-hydroxypiperidine (2.00 g) and 4-chloropyridine 1-oxide (1.12 g), was added sodium hydrogencarbonate (1.75 g) and the mixture was heated under reflux for 4 hours. The reaction mixture was allowed to cool and water was added thereto. The reaction mixture was extracted with methylene chloride and the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: methylene chloride : methanol = 9:1 - 4:1) to obtain the title compound (1.03 g).

NMR spectrum (\*DMSO-d<sub>6</sub>) δppm: 7.90-7.83(2H,m), 6.92-6.84(2H,m), 6.78-6.70(1H,m), 4.58(1H,brs), 3.64-3.50(2H,m), 3.17-3.04(2H,m), 2.92(2H,d,J=6Hz), 1.60-1.30(4H,m), 1.35(9H,s)

<Step A-2>

Synthesis of 4-[(t-butoxycarbonylamino)methyl]-4-hydroxy-1-(4-pyridyl)piperidine

**[0309]** Raney nickel (catalytic amount) prepared by the procedure described in the literature: "Aromatic Amine Oxide" (Eiji Ochiai, Elsevier, page 189, 1967) was added to a solution of the compound obtained in Step A-1 (300 mg) in methanol (3 ml). The mixture was stirred at room temperature for 3.5 hours under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent: methylene chloride : methanol = 4:1) to obtain the title compound (214 mg).

NMR spectrum (\*DMSO-d<sub>6</sub>) δppm: 8.10(2H,d,J=7Hz), 6.87(2H,d,J=7Hz), 6.76-6.68(1H,m), 4.55(1H,brs), 3.78-3.65(2H,m), 3.24-3.11(2H,m), 2.92(2H,d,J=6Hz), 1.58-1.30(4H,m), 1.35(9H,s)

<Step A-3>

Synthesis of 4-(aminomethyl)-4-hydroxy-1-(4-pyridyl)piperidine hydrochloride

**[0310]** The compound obtained in Step A-2 (175 mg) was dissolved in 10% hydrogen chloride-methanol solution (2 ml) and the solution was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was solidified by addition of diethyl ether, and thereafter fully triturated. The solvent was distilled off under reduced pressure to obtain the title compound (160 mg).

NMR spectrum (\*DMSO-d<sub>6</sub>) δppm: 13.68(1H,brs), 8.20(2H,d,J=8Hz), 8.13(2H,brs), 7.22(2H,d,J=8Hz), 5.43(1H,s), 4.08-3.96(2H,m), 3.52-3.32(2H,m), 2.80(2H,brs), 1.77-1.46(4H,m)

<Step A-4>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0311]** The procedure of Example 1 <Step A-3> was repeated by using the compound obtained in Step A-3 instead of 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine and chloroform-ethanol instead of toluene to obtain the title compound. HRMS: C<sub>28</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 584.1496, Found: 584.1459

<Step B-1>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0312]** To a solution of the compound obtained in Example 1 <Step A-3> (4.00 g) in 1,2-dichloroethane (42 ml) were added 1,8-bis(N,N-dimethylamino)naphthalene (287 mg) and 1-chloroethyl chloroformate (1.82 ml) and the mixture

was heated under reflux for 1 hour. The reaction mixture was allowed to cool and purified by silica gel column chromatography (eluent; methylene chloride : methanol = 8:1) to obtain a solid. The solid (4.29 g) was dissolved in methanol (43 ml) and the solution was heated under reflux for 30 minutes. The reaction mixture was concentrated and to the resulting residue was added 1N aqueous solution of sodium hydroxide. The mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (3.47 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.38-8.34(1H,m), 7.99-7.92(3H,m), 7.82-7.76(1H,m), 7.65-7.58(1H,m), 4.43(1H,d, J=12Hz), 4.45-4.30(2H,m), 4.27(1H,d,J=12Hz), 4.19(1H,d,J=12Hz), 3.34(1H,d,J=17Hz), 3.08(1H,d,J=12Hz), 3.04-2.82(2H,m), 2.77-2.61(2H,m), 2.33(1H,d,J=12Hz), 2.12(3H,s), 1.86-1.67(2H,m), 1.47-1.29(2H,m)

<Step B-2>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

[0313] The procedure of Example 1 <Step A-7> was repeated by using the compound obtained in Step B-1 (2.60 g) to obtain the title compound (240 mg).

(Example 8)

Synthesis of 1,4-diaza-4-[6-chloronaphthalen-2-ylsulfonyl]-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one

<Step 1>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one

[0314] To a solution in toluene (1 L) of the compound obtained in Example 1 <Step A-2> (3.77 g) and the conventionally known compound: 4-(aminomethyl)-1-benzyl-4-(hydroxymethyl)piperidine (2.00 g) was added p-toluenesulfonic acid monohydrate (162 mg) and the mixture was heated under reflux for 1 hour using a Dean Stark. After allowing the reaction mixture to cool, saturated aqueous solution of sodium hydrogencarbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 40:1) to obtain the title compound (1.53 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.35(1H,s), 7.97-7.90(3H,m), 7.82-7.76(1H,m), 7.63-7.56(1H,m), 7.33-7.18(5H,m), 5.03(1H,d,J=13Hz), 4.68(1H,d,J=14Hz), 4.32-4.20(2H,m), 4.06(1H,d,J=13Hz), 3.67(1H,d,J=12Hz), 3.54-3.43(1H,m), 3.46(2H,s), 3.32(1H,d,J=16Hz), 2.54(1H,d,J=14Hz), 2.46(1H,d,J=12Hz), 2.45-2.35(2H,m), 2.32-2.19(2H,m), 2.13(3H,s), 1.54-1.24(4H,m)

<Step 2>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one

[0315] To a solution of the compound obtained in Step 1 (76.6 mg) in methanol (2 ml) was added 1N aqueous solution of sodium hydroxide (2.84 ml) at room temperature. The reaction mixture was stirred at room temperature for 20 minutes and the solvent was distilled off under reduced pressure. Water was added to the residue and the mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (63.1 mg).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.36-8.32(1H,m), 7.96-7.90(3H,m), 7.81-7.75(1H,m), 7.63-7.57(1H,m), 7.32-7.18(5H,m), 4.73-4.62(1H,m), 4.34-4.15(3H,m), 3.90-3.80(1H,m), 3.68-3.44(2H,m), 3.46(2H,s), 3.34(1H,d,J=17Hz), 2.51(1H,d,J=14Hz), 2.47-2.36(3H,m), 2.32-2.20(2H,m), 2.14-2.07(1H,m), 1.58-1.28(4H,m)

<Step 3>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one

**[0316]** To a solution in methylene chloride (30 ml) of the compound obtained in Step 2 (1.20 g), benzyltriethylammonium chloride (39.0 mg) and dimethyl sulfate (260 ml), was gradually added 50% aqueous solution of sodium hydroxide (7.5 ml) with vigorous stirring under cooling with ice. The reaction mixture was stirred at room temperature for 45 minutes, adjusted to pH 9 with saturated aqueous solution of ammonium chloride under cooling with ice and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 30:1) to obtain the title compound (541 mg). NMR spectrum ( $^1\text{H}$ ,  $\text{CDCl}_3$ )  $\delta$ ppm: 8.34(1H,s), 7.96-7.89(3H,m), 7.81-7.75(1H,m), 7.62-7.56(1H,m), 7.35-7.17(5H,m), 4.67(1H,d,J=14Hz), 4.35-4.23(2H,m), 4.04(1H,d,J=11Hz), 3.69-3.42(5H,m), 3.47(3H,s), 3.29(1H,d,J=17Hz), 2.55(1H,d,J=14Hz), 2.49-2.19(5H,m), 1.58-1.23(4H,m)

<Step 4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one hydrochloride

**[0317]** To a suspension in 1,2-dichloroethane (10 ml) of the compound obtained in Step 3 (200 mg) and 1,8-bis(dimethylamino)naphthalene (15.0 mg) was added 1-chloroethyl chloroformate (92.0 ml) and the mixture was heated under reflux for 30 minutes. The mixture was allowed to cool and thereafter purified by silica gel column chromatography (eluent; methylene chloride : methanol = 20:1). The solvent was distilled off under reduced pressure. To the residue was added methanol (10 ml) and the mixture was heated under reflux for 30 minutes. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure and the resulting residue was crystallized by addition of diethyl ether. The supernatant was removed by decantation. The solvent was distilled off under reduced pressure to obtain the title compound (167 mg).

NMR spectrum ( $^1\text{H}$ ,  $\text{DMSO}-d_6$ )  $\delta$ ppm: 8.71(2H,brs), 8.60(1H,s), 8.35-8.14(3H,m), 7.94-7.83(1H,m), 7.80-7.68(1H,m), 4.36(1H,d,J=14Hz), 4.21-4.09(2H,m), 3.98-3.88(2H,m), 3.77-2.72(7H,m), 3.32(3H,s), 2.79(1H,d,J=14Hz), 2.67(1H,d,J=12Hz), 1.62-1.42(4H,m)

<Step 5>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.4.0]decane-9,4'-piperidin]-2-one

**[0318]** To a suspension in 2-ethoxyethanol (3 ml) of the compound obtained in Step 4 (50.0 mg) and 4-chloropyridine hydrochloride (14 mg), was added diisopropylethylamine (57.0 ml) and the mixture was heated under reflux for 4 hours. After allowing the reaction mixture to cool, potassium carbonate (78.0 mg) was added and the mixture was stirred for 1 hour. The insoluble content was removed by filtration and the filtrate was concentrated. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 10:1 - 5:1). Then, the residue was purified by silica gel column chromatography [ChromatorexNH<sup>TM</sup>] (eluent; ethyl acetate) to obtain the title compound (7.4 mg). HRMS:  $\text{C}_{28}\text{H}_{31}\text{ClN}_4\text{O}_5\text{S}(\text{M}^+)$ : Calculated: 570.1703, Found: 570.1658.

(Example 9)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of ethyl 2-[(2,2-diethoxyethyl)amino]acetate

**[0319]** To a suspension of the glycine ethyl ester hydrochloride (1.00 g) and bromoacetaldehyde diethyl acetal (1.08 ml) in N,N-dimethylformamide (30 ml), were added cesium carbonate (4.67 g) and sodium iodide (107 mg) and the mixture was stirred at 100 °C for 4 hours. The reaction mixture was adjusted to pH 2 with 1N hydrochloric acid and

washed with ethyl acetate. The aqueous layer was adjusted to pH 11 with 1N aqueous solution of sodium hydroxide and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and thereafter the solvent was distilled off under reduced pressure to obtain the title compound (860 mg).

NMR spectrum (CDCl<sub>3</sub>) δppm: 4.63-4.57(1H,m), 4.24-4.14(2H,m), 3.78-3.64(2H,m), 3.61-3.48(2H,m), 3.44(2H,s), 2.76(2H,d,J=6Hz), 1.32-1.15(9H,m)

<Step 2>

Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)(2,2-diethoxyethyl)amino]acetate

**[0320]** The compound obtained in Step 1 (504 mg) was suspended in methylene chloride (20 ml) and to the suspension were added triethylamine (336 ml) and then 6-chloronaphthalene-2-sulfonyl chloride (600 mg) under cooling with ice. After stirring the mixture overnight at room temperature, saturated sodium chloride solution was added and the mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and thereafter the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate =20:1 - 4:1) to obtain the title compound (750 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.40(1H,s), 7.93-7.82(4H,m), 7.55(1H,dd,J=2,9Hz), 4.68-4.63(1H,m), 4.33(2H,s), 3.96(2H,q,J=7Hz), 3.77-3.64(2H,m), 3.60-3.47(2H,m), 3.37(2H,d,J=6Hz), 1.23-1.13(6H,m), 1.12-1.04(3H,m)

<Step 3>

Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)(formylmethyl)amino]acetate

**[0321]** To a mixed solution of trifluoroacetic acid (5 ml), chloroform (1.5 ml) and water (2.5 ml) was added a solution of the compound obtained in Step 2 (560 mg) in chloroform (1 ml) under cooling with ice water. After stirring for 1.5 hours under cooling with ice water, the reaction mixture was adjusted to pH 8 with saturated aqueous solution of sodium hydrogencarbonate and extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate and thereafter the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 5:1 - 2:1) to obtain the title compound (240 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 9.74-9.70(1H,m), 8.39(1H,s), 7.98-7.85(3H,m), 7.85-7.78(1H,m), 7.62-7.53(1H,m), 4.24-4.03(6H,m), 1.21-1.13(3H,m)

<Step 4>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0322]** To a solution in toluene (25 ml) of the compound obtained in Step 3 (200 mg) and 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine (119 mg) was added p-toluenesulfonic acid monohydrate (5.0 mg) and the mixture was heated under reflux for 1 hour using a Dean Stark. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain the title compound (200 mg).

NMR spectrum (CDCl<sub>3</sub>) δppm: 8.36-8.32(1H,m), 7.97-7.88(3H,m), 7.81-7.74(1H,m), 7.60(1H,dd,J=2,9Hz), 7.37-7.21(5H,m), 5.17-5.10(1H,m), 4.41-4.24(2H,m), 3.65(1H,d,J=12Hz), 3.49(2H,s), 3.28(1H,d,J=17Hz), 3.16(1H,d,J=12Hz), 2.60-2.32(5H,m), 1.92-1.58(4H,m)

<Step 5>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one hydrochloride

**[0323]** The procedure of Example 1 <Step A-6> was repeated by using the compound obtained in Step 4 (180 mg) to obtain the title compound (162 mg).

NMR spectrum (DMSO-d<sub>6</sub>) δppm: 9.00-8.57(3H,m), 8.33-8.13(3H,m), 7.98-7.87(1H,m), 7.75(1H,dd,J=2,9Hz), 5.16(1H,dd,J=4,8Hz), 4.22-4.08(1H,m), 4.05(1H,d,J=16Hz), 3.81-3.69(1H,m), 3.62-2.78(6H,m), 2.78-2.64(1H,m), 2.05-1.58(4H,m)

<Step 6>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0324]** The procedure of Example 1 <Step A-7> was repeated by using the compound obtained in Step 5 (100 mg) to obtain the title compound (3.8 mg).

HRMS:  $C_{25}H_{25}ClN_4O_4S(M^+)$ : Calculated: 512.1285, Found: 512.1310

(Example 10)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-[2-(methylthio)pyrimidin-4-yl]spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0325]** The procedure of Example 2 <Step 1> was repeated by using the compound obtained in Example 9 <Step 5> to obtain the title compound (293 mg).

NMR spectrum ( $CDCl_3$ )  $\delta$ ppm: 8.42-8.35(1H,m), 8.07-7.92(3H,m), 8.02(1H,d,J=6Hz), 7.84-7.76(1H,m), 7.68-7.58(1H,m), 6.21(1H,d,J=6Hz), 5.21(1H,dd,J=4,9Hz), 4.45-4.34(1H,m), 4.33(1H,d,J=17Hz), 4.12-3.93(2H,m), 3.80-3.71(1H,m), 3.52-3.27(2H,m), 3.32(1H,d,J=17Hz), 3.23-3.15(1H,m), 2.48(3H,s), 2.57-2.39(1H,m), 2.23-1.80(1H,m), 1.80-1.57(3H,m)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0326]** The procedure of Example 2 <Step 2> was repeated by using the compound obtained in Step 1 (290 mg) to obtain the title compound (15.0 mg).

HAMS:  $C_{24}H_{24}ClN_5O_4S(M^+)$ : Calculated: 513.1237, Found: 513.1276

(Example 11)

Synthesis of 1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of ethyl 2-(((E)-4-chlorostyrylsulfonyl)(2,2-diethoxyethyl)amino)acetate

**[0327]** The compound obtained in Example 9 <Step 1> (2.46 g) was suspended in methylene chloride (90 ml) and to the suspension were added triethylamine (1.56 ml) and then (E)-4-chlorostyrylsulfonyl chloride (2.26 g) under cooling with ice. The mixture was stirred at room temperature for 4 hours and water was added thereto. The mixture was extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and thereafter the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 5:1) to obtain the title compound (2.03 g).

NMR spectrum ( $^1CDCl_3$ )  $\delta$ ppm: 7.48-7.35(5H,m), 6.96-6.88(1H,m), 4.64(1H,t,J=5Hz), 4.29(2H,s), 4.17(2H,q,J=7Hz), 3.78-3.47(4H,m), 3.24(2H,d,J=5Hz), 1.32-1.14(9H,m)

<Step 2>

Synthesis of ethyl 2-(((E)-4-chlorostyrylsulfonyl)(formylmethyl)amino)acetate

**[0328]** To a mixed solution of the compound obtained in Step 1 (2.00 g), chloroform (9.5 ml) and water (9.5 ml) was

added trifluoroacetic acid (13.5 ml) under cooling with ice water. The reaction mixture was stirred at room temperature for 4 hours, adjusted to pH 8 with saturated aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and thereafter the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 2:1) to obtain the title compound (1.27 g). NMR spectrum (CDCl<sub>3</sub>) δppm: 9.68(1H,s), 7.50-7.35(5H,m), 6.82(1H,d,J=15Hz), 4.25-4.10(6H,m), 1.32-1.21(3H,m)

<Step 3>

Synthesis of 1,4-diaza-1'-benzyl-4-((E)-4-chlorostyrylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0329]** To a solution in toluene (175 ml) of the compound obtained in Step 2 (1.27 g) and 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine (810 mg) was added p-toluenesulfonic acid monohydrate (35.0 mg) and the mixture was heated under reflux for 1 hour using a Dean Stark. The reaction mixture was allowed to cool and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain the title compound (1.08 g).

NMR spectrum (CDCl<sub>3</sub>) δppm: 7.48(1H,d,J=15Hz), 7.49-7.37(4H,m), 7.37-7.22(5H,m), 6.63(1H,d,J=15Hz), 5.13(1H,dd,J=4,9Hz), 4.32-4.18(2H,m), 3.74(1H,d,J=12Hz), 3.56 (1H,d,J=17Hz), 3.51(2H,s), 3.20(1H,d,J=12Hz), 2.75-2.64(1H,m), 2.61-2.36(4H,m), 1.94-1.66(4H,m)

<Step 4>

Synthesis of 1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one hydrochloride

**[0330]** The procedure of Example 1 <Step A-6> was repeated by using the compound obtained in Step 3 (1.00 g) to obtain the title compound (914 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 9.68(2H,brs), 7.49(1H,d,J=15Hz), 7.58-7.31(4H,m), 6.66(1H,d,J=15Hz), 5.21-5.12(1H,m), 4.33-4.14(2H,m), 3.93(1H,d,J=12Hz), 3.59(1H,d,J=17Hz), 3.54-3.10(4H,m), 3.23(1H,d,J=12Hz), 2.80-2.68(1H,m), 2.35-2.00(2H,m), 1.92-1.65(2H,m)

<Step 5>

Synthesis of 1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0331]** The procedure of Example 1 <Step A-7> was repeated by using the compound obtained in Step 4 (350 mg) to obtain the title compound (46.0 mg).

HRMS:C<sub>23</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>4</sub>S(M<sup>+</sup>): Calculated: 488.1285, Found: 488.1306

(Example 12)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0332]** To a solution of the compound obtained in Example 1 (111 mg) in methanol (0.4 ml) was added methanesulfonic acid (0.01313.6 ml) and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure and the residue was crystallized by addition of diethyl ether. The supernatant was removed by decantation and the solvent was distilled off under reduced pressure to obtain the title compound (119 mg).

(Example 13)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0333]** The procedure of Example 12 was repeated by using the (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one (111 mg) produced by the optical resolution method described in Example 1 <Step A-7> to obtain the title compound (119 mg).

(Example 14)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0334]** The procedure of Example 12 was repeated by using the compound obtained in Example 3 <Step A-2> (33.0 mg) to obtain the title compound (38.0 mg).

(Example 15)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0335]** The procedure of Example 12 was repeated by using the compound obtained in Example 4 <Step A-3> (40.0 mg) to obtain the title compound (43.0 mg).

(Example 16)

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0336]** The procedure of Example 12 was repeated by using the compound obtained in Example 7 <Step A-4> (33.0 mg) to obtain the title compound (34.2 mg).

(Example 17)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0337]** The procedure of Example 12 was repeated by using the compound obtained in Example 9 <Step 6> (27.8 mg) to obtain the title compound (30.0 mg).

(Example 18)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0338]** The procedure of Example 12 was repeated by using the compound obtained in Example 10 <Step 2> (31.2 mg) to obtain the title compound (34.0 mg).

(Example 19)

Synthesis of 1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0339]** The procedure of Example 12 was repeated by using the compound obtained in Example 11 <Step 5> (30.6 mg) to obtain the title compound (31.5 mg).

(Example 20)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0340]** The procedure of Example 4 <Step A-1> was repeated by using the compound obtained in Example 1 <Step B-1> (4.00 g) to obtain the title compound (3.90 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36-8.31(1H,m), 7.98-7.90(3H,m), 7.81-7.74(1H,m), 7.65-7.57(1H,m), 7.40-7.24(5H,m), 5.10(2H,s), 4.40-4.06(7H,m), 3.89(1H,d,J=10Hz), 3.78(1H,d,J=10Hz), 3.82-3.20(6H,m), 2.29(1H,d,J=12Hz), 2.03-1.91(1H,m), 1.84-1.70(1H,m), 1.46-1.24(5H,m)

<Step 2>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-hydroxyethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0341]** The compound obtained in Step 1 (100 mg) was dissolved in a mixed solution of tetrahydrofuran (1 ml) and ethanol (1 ml) and to the solution were added lithium chloride (18.6 mg) and sodium borohydride (16.5 mg). After stirring at room temperature for 3 hours, saturated aqueous solution of ammonium chloride was added to the reaction mixture under cooling with ice, followed by extraction with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent;methylene chloride: methanol = 40:1 - 20:1) to obtain the title compound (86.4 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.37-8.33(1H,m), 7.98-7.92(3H,m), 7.78(1H,dd,J=2,9Hz), 7.64-7.58(1H,m), 7.39-7.24(5H,m), 5.10(2H,s), 4.50(1H,d,J=12Hz), 4.38(1H,d,J=17Hz), 4.21(1H,d,J=12Hz), 3.86(1H,d,J=10Hz), 3.83-3.26(9H,m), 3.60(1H,d,J=10Hz), 3.13(1H,d,J=12Hz), 2.40-2.33(1H,m), 2.24(1H,d,J=12Hz), 1.90-1.70(2H,m), 1.46-1.33(2H,m)

<Step 3>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0342]** The procedure of Example 1 <Step B-2> was repeated by using the compound obtained in Step 2 (50 mg) to obtain the title compound (35 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36-8.32(1H,m), 7.98-7.90(3H,m), 7.80-7.74(1H,m), 7.61(1H,dd,J=2,9Hz), 7.40-7.26(5H,m), 5.10(2H,s), 4.40-4.26(2H,m), 4.13(1H,d,J=11Hz), 3.36(3H,s), 3.82-3.20(12H,m), 2.27(1H,d,J=12Hz), 1.98-1.66(2H,m), 1.46-1.30(2H,m)

<Step 4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0343]** The procedure of Example 1 <Step B-3> was repeated by using the compound obtained in Step 3 (2.00 g) to obtain the title compound (1.54 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38-8.32(1H,m), 7.99-7.91(3H,m), 7.81-7.75(1H,m), 7.64-7.58(1H,m), 4.39-4.16(3H,m), 3.80-3.66(4H,m), 3.60-3.51(2H,m), 3.37(3H,s), 3.31(1H,d,J=17Hz), 3.17(1H,d,J=11Hz), 3.10-2.99(1H,m), 2.96-2.84(1H,m), 2.76-2.60(2H,m), 2.27(1H,d,J=12Hz), 1.96-1.62(2H,m), 1.48-1.27(2H,m)



<Step 5>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0344]** To a solution in ethanol (14 mg) of the compound obtained in Step 4 (700 mg) and 4-chloropyridine hydrochloride (201 mg) was added diisopropylethylamine (1.17 ml) and the mixture was stirred in a sealed tube at 150°C for 15 hours. The reaction mixture was allowed to cool and concentrated. The resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 20:1 - 10:1) to obtain the title compound (140 mg).  
HRMS: C<sub>29</sub>H<sub>33</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 600.1809, Found: 600.1785

(Example 21)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0345]** The procedure of Example 12 was repeated by using the compound obtained in Example 20 <Step 5> (50.0 mg) to obtain the title compound (59.3 mg).

(Example 22)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-hydroxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0346]** The procedure of Example 20 <Step 2> was repeated by using the compound obtained in Example 4 <Step A-3> (50.0 mg) to obtain the title compound (39.2 mg).  
HRMS: C<sub>28</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 586.1652, Found: 586.1685

(Example 23)

Synthesis of 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-2-oxospiro[bicyclo[4.3.0]nonane-8,4'-piperidin-1'-yl]]-1-methylpyridinium p-toluenesulfonate

**[0347]** The compound obtained in Example 1 <Step A-7> was dissolved in a mixed solution of methanol (2 ml) - chloroform (1 ml) and to the solution were added silica gel (50 mg) and methyl p-toluenesulfonate (36.8 mg). Thereafter, the mixture was heated under reflux all day long. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 10:1 - 5:1) to obtain the title compound (65.3 mg).  
IR (KBr) cm<sup>-1</sup>: 3435, 3066, 1657, 1554, 1205, 1122

(Example 24)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]

**[0348]** To a suspension of the compound obtained in Example 1 <Step A-7> (100 mg) in tetrahydrofuran (2 ml) was added a borane-tetrahydrofuran complex (1.0 N tetrahydrofuran solution, 0.54 ml) under cooling with ice. After stirring the mixture for 1 hour under cooling with ice, 10% hydrochloric acid-methanol solution was added and the mixture was stirred for 15 minutes under cooling with ice. The solvent was distilled off under reduced pressure. The resulting residue was adjusted to pH 9 with saturated aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off under reduced pressure. The resulting residue was purified by thin-layer chromatography (developer; methylene chloride : methanol = 10:1) to obtain the title compound (14.6 mg).

(Example 25)

**[0349]** Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0350]** To a solution of the compound obtained in Example 1 <Step B-1> (6834.0 g) in methylene chloride (68340 ml) were added 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxylbenzoate and a free radical (314 mg). 5% Aqueous solution of sodium hydrogencarbonate (1.36 ml) was added dropwise with stirring under cooling with ice and bleaching powder (54.0 g) was added. The mixture was vigorously stirred for 1.5 hours under cooling with ice, adjusted to pH 1 with 1N hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (62.7 g).

NMR spectrum (\*CD<sub>3</sub> OD) δppm: 8.52-8.44(1H,m), 8.15-7.97(3H,m), 7.83(1H,dd,J=2,9Hz), 7.63(1H,dd,J=2,9Hz), 7.41-7.25(5H,m), 5.08(2H,s), 4.69-4.61(1H,m), 4.18(1H,d,J=17Hz), 4.03(1H,d,J=12Hz), 3.82-3.64(2H,m), 3.57-3.17(3H,m), 3.44(1H,d,J=17Hz), 2.79-2.66(1H,m), 1.87-1.39(4H,m),

<Step 2>

Synthesis of 1,4-diaza-1'-(benzyloxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0351]** To a solution of the compound obtained in Step 1 (62.7g) in pyridine (640 ml) was added ethanol (58.4 ml). After gradually adding p-toluenesulfonyl chloride (97.3 g) with stirring under cooling with ice, the mixture was stirred at room temperature for 4 hours. After addition of ice water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water, dilute hydrochloric acid and saturated sodium chloride solution, and thereafter dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 3:1 - 2:1) to obtain the title compound (40.1 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.35(1H,s), 7.99-7.87(3H,m), 7.80-7.72(1H,m), 7.65-7.56(1H,m), 7.40-7.28(5H,m), 5.10(2H,s), 4.75(1H,d,J=12Hz), 4.38-4.18(3H,m), 4.07(1H,d,J=12Hz), 3.81-3.58(2H,m), 3.48-3.22(4H,m), 2.45(1H,d,J=12Hz), 1.75-1.60(2H,m), 1.56-1.42(2H,m), 1.39-1.30(3H,m)

<Step 3>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0352]** The procedure of Example 1 <Step B-3> was repeated by using the compound obtained in Step 2 (40.0 g) to obtain the title compound (29.7 g).

NMR spectrum (CDCl<sub>3</sub>) δppm: 8.38-8.31(1H,m), 8.01-7.85(3H,m), 7.77(1H,dd,J=2,9Hz), 7.61(1H,dd,J=2,9Hz), 4.74(1H,d,J=11Hz), 4.38-4.17(3H,m), 4.11(1H,d,J=12Hz), 3.41-3.26(2H,m), 3.16-2.77(4H,m), 2.45(1H,d,J=11Hz), 1.90-1.45(4H,m), 1.34(3H,t,J=7Hz)

<Step 4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0353]** The procedure of Example 20 <Step 5> was repeated by using the compound obtained in Step 3 (30.0 g) to obtain the title compound (14.2 g).

HRMS:C<sub>28</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 584.1496, Found: 584.1532

(Example 26)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0354]** The procedure of Example 12 was repeated by using the compound obtained in Example 25 <Step 4> (56.0

mg) to obtain the title compound (58.9 mg).

(Example 27)

- 5 Synthesis of 1,4-diaza-6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

10 **[0355]** To a solution of the compound obtained in Example 25 <Step 4> (400 mg) in methanol (9.6 ml) was added 1N aqueous solution of sodium hydroxide (2.74 ml) under cooling with ice and the mixture was stirred at room temperature for 1 hour. After adjusting the mixture to pH 4 with 1N hydrochloric acid, the precipitated solid was collected by filtration, washed with water and dried in vacuum to obtain the title compound (335 mg).  
IR(KBr)cm<sup>-1</sup>:1666, 1647, 1537, 1460, 1350, 1169, 698

(Example 28)

- 15 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

20 **[0356]** To a solution of the compound obtained in Example 27 (20.0 mg) in pyridine (0.20 ml) was added methanol (0.015 ml). After gradually adding p-toluenesulfonyl chloride (34.2 mg), the mixture was stirred at room temperature for 0.5 hour. After addition of saturated aqueous solution of sodium hydrogencarbonate, the reaction mixture was extracted with methylene chloride and the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 15:1 - 10:1) to obtain the title compound (17.1 mg).  
25 IR(KBr)cm<sup>-1</sup>:1751, 1678, 1597, 1350, 1165, 1080

(Example 29)

- 30 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(isopropoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0357]** The procedure of Example 28 was repeated by using the compound obtained in Example 27 (20 mg) and using isopropyl alcohol (0.028 ml) instead of methanol to obtain the title compound (18.1 mg).  
HRMS:C<sub>29</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 598.1652, Found: 598.1668

(Example 30)

- 40 Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(propoxycarbonyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0358]** The procedure of Example 28 was repeated by using the compound obtained in Example 27 (20 mg) and using n-propyl alcohol (0.026 ml) instead of methanol to obtain the title compound (15.3 mg).  
HRMS:C<sub>29</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 598.1652, Found: 598.1625

(Example 31)

- 45 Synthesis of 6-(allyloxycarbonyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

50 **[0359]** The procedure of Example 28 was repeated by using the compound obtained in Example 27 (20 mg) and using allyl alcohol (0.025 ml) instead of methanol to obtain the title compound.  
IR(KBr)cm<sup>-1</sup>:1747, 1678, 1597, 1350, 1167, 972

55

(Example 32)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0360]** The procedure of Example 28 was repeated by using the compound obtained in Example 27 (20 mg) and using 2-methoxyethanol (0.028 ml) instead of methanol to obtain the title compound (13.1 mg).

HRMS:  $C_{29}H_{31}ClN_4O_7$  S(M<sup>+</sup>): Calculated: 614.1602, Found: 614.1597

(Example 33)

Synthesis of 1,4-diaza-6-(t-butoxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0361]** Dioxane (1.0 ml) solidified in a bath cooled to -20 °C was added concentrated sulfuric acid (0.1 ml). The mixture was warmed to room temperature to obtain a homogenous solution. The solution was solidified again in the bath cooled to -20 °C and the compound obtained in Example 27 (18.0 mg) was added. The mixture was warmed to room temperature to obtain a homogenous solution, which was solidified in the bath cooled to -20 °C. After adding liquid isobutylene (0.7 ml), the mixture was stirred in a sealed tube at room temperature for 5 hours. Saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 15:1) to obtain the title compound (17.1 mg). HRMS:  $C_{30}H_{33}ClN_4O_6$  S(M<sup>+</sup>): Calculated: 612.1809, Found: 612.1786

(Example 34)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-[1-(ethoxycarbonyloxy)ethoxycarbonyl]-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0362]** To a solution of the compound obtained in Example 27 (42.0 mg) in N,N-dimethylformamide (2.1 ml) were added triethylamine (0.063 ml) and 1-iodochloroethylethyl carbonate (0.0164 ml) and the mixture was stirred at room temperature for 2 days. After adding water to the reaction mixture and extracting with methylene chloride, the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 15:1) to obtain the title compound (11.6 mg).

IR(KBr)cm<sup>-1</sup>: 1765, 1670, 1645, 1599, 1543, 1167

(Example 35)

Syntheses of (+)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one and (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0363]** The compound obtained in Example 25 <Step 4> was optically resolved on HPLC [column used, Daicel Chiralcel OD manufactured by Daicel Chemical Industries, Ltd., 0.46 cm x 25 cm; eluent; n-hexane : ethanol = 1:1; flow rate, 1.0 ml/min, detection wavelength, 254 nm] to obtain the (+) form of the title compound [retention time: 12.7 min,  $[\alpha]^{33}_D$  +99.7 (c1.000, ethanol)] and the (-) form of the title compound [retention time: 14.9 min,  $[\alpha]^{33}_D$  -99.3 (c1.000, ethanol)], respectively.

**[0364]** In addition, to a solution of the compound obtained in Example 25 <Step 4> (845 mg) in methanol (20 ml) was added (-)-O,O'-dibenzoyl-LD-tartaric acid (543 mg) and the mixture was stirred at room temperature for 1 hour. The precipitate was collected by filtration and air-dried. The thus obtained crystals (598 mg) were suspended in methanol (15 ml) and heated under reflux for 10 minutes. After allowing the suspension to cool, the precipitate was collected by filtration and air-dried. The thus obtained crystals (386 mg) were dissolved in saturated aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure to thereby obtain the (-) form of the title compound (230 mg, 97.2% ee). The same procedure was repeated by using (+)-O,O'-dibenzoyl-D-tartaric acid to obtain the (+) form of the title compound.

(+) form: HRMS:  $C_{26}H_{29}ClN_4O_6S(M^+)$ : Calculated: 584.1496, Found: 584.1462  
 (-) form: HRMS:  $C_{28}H_{29}ClN_4O_6S(M^+)$ : Calculated: 584.1496, Found: 584.1540

(Example 36)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0365]** The procedure of Example 12 was repeated by using the (-) form of the compound obtained in Example 35 (100 mg) to obtain the title compound (104 mg).

(Example 37)

Synthesis of (-)-1,4-diaza-6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0366]** The procedure of Example 27 was repeated by using the compound obtained in Example 35 (1.80 g) to obtain the title compound (1.63 g).

IR(KBr)  $cm^{-1}$ : 1664, 1647, 1543, 1460, 1350, 1169

(Example 38)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0367]** The procedure of Example 28 was repeated by using the compound obtained in Example 37 (160 mg) to obtain the title compound (153 mg).

IR(KBr)  $cm^{-1}$ : 1749, 1678, 1599, 1349

(Example 39)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(isopropoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0368]** The procedure of Example 28 was repeated by using the compound obtained in Example 37 (150 mg) and using isopropyl alcohol (0.206 ml) instead of methanol to obtain the title compound (147.7 mg).

HRMS:  $C_{29}H_{31}ClN_4O_6S(M^+)$ : Calculated: 598.1652, Found: 598.1667

(Example 40)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(propoxycarbonyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0369]** The procedure of Example 28 was repeated by using the compound obtained in Example 37 (170 mg) and using n-propyl alcohol (0.023 ml) instead of methanol to obtain the title compound (158 mg).

HRMS:  $C_{29}H_{31}ClN_4O_6S(M^+)$ : Calculated: 598.1652, Found: 598.1666

(Example 41)

Synthesis of (-)-6-(allyloxycarbonyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0370]** The procedure of Example 28 was repeated by using the compound obtained in Example 37 (160 mg) and using allyl alcohol (0.196 ml) instead of methanol to obtain the title compound (158 mg).

IR (KBr)  $cm^{-1}$ : 1747, 1678, 1597, 1419, 1352

(Example 42)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0371]** The procedure of Example 28 was repeated by using the compound obtained in Example 37 (180 mg) and using 2-methoxyethanol (0.255 ml) instead of methanol to obtain the title compound (178.6 mg).

HRMS:  $C_{29}H_{31}ClN_4O_7$  S(M<sup>+</sup>): Calculated: 614.1602, Found: 614.1572

(Example 43)

Synthesis of (-)-1,4-diaza-6-(t-butoxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0372]** The procedure of Example 33 was repeated by using the compound obtained in Example 37 (160 mg) to obtain the title compound (146 mg).

IR(KBr)cm<sup>-1</sup>: 1738, 1678, 1597, 1352, 1157, 1132

(Example 44)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0373]** The procedure of Example 12 was repeated by using the compound obtained in Example 38 (110 mg) to obtain the title compound (12 mg).

(Example 45)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(isopropoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0374]** The procedure of Example 12 was repeated by using the compound obtained in Example 39 (110 mg) to obtain the title compound (125 mg).

(Example 46)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(propoxycarbonyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0375]** The procedure of Example 12 was repeated by using the compound obtained in Example 40 (110 mg) to obtain the title compound (126 mg).

(Example 47)

Synthesis of (-)-6-(allyloxycarbonyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0376]** The procedure of Example 12 was repeated by using the compound obtained in Example 41 (110 mg) to obtain the title compound (129 mg).

(Example 48)

Synthesis of (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0377]** The procedure of Example 12 was repeated by using the compound obtained in Example 42 (110 mg) to obtain the title compound (127 mg).

(Example 49)

Synthesis of (-)-1,4-diaza-6-(t-butoxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0378]** The procedure of Example 12 was repeated by using the compound obtained in Example 43 (119 mg) to obtain the title compound (137 mg).

(Example 50)

Synthesis of ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate

**[0379]** To a solution of the compound obtained in Example 25 <Step 4> (100 mg) in methanol (2.4 ml) was added 1N aqueous solution of sodium hydroxide (0.684 ml) at room temperature. The mixture was stirred for 1 hour and adjusted to pH 2-3 with 1N hydrochloric acid. Thereafter, the solvent was distilled off under reduced pressure and the resulting residue was dissolved in methanol (5 ml) and ion-exchange resin MSC-1 (100-200 mesh, H-form, manufactured by Muromachi Chemicals Inc., 2.0 g) was added and the mixture was stirred for 30 minutes. The resin was collected by filtration, washed with methanol and added to 2N ammonia - methanol solution (5 ml). The mixture was stirred for 30 minutes. The solution obtained by filtering off the resin was concentrated under reduced pressure to obtain the title compound (54.8 mg).

IR(KBr)cm<sup>-1</sup>:1657, 1628, 1601, 1396, 1348, 1169

(Example 51)

Syntheses of (+)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate and (-)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate

**[0380]** The procedure of Example 50 was repeated by using the (+) form of the compound obtained in Example 35 (40.0 mg) to obtain the (+) form of the title compound (20.5 mg).

IR(KBr)cm<sup>-1</sup>:1626, 1603, 1398, 1348, 1169

**[0381]** Further, the procedure of Example 50 was repeated by using the (-) form of the compound obtained in Example 35 (55.0 mg) to obtain the (-) form of the title compound (28.3 mg). IR(KBr)cm<sup>-1</sup>:1657, 1626, 1603, 1396, 1348, 1169

(Example 52)

Synthesis of 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-2-exospire[bicyclo[4.3.0]nonane-8,4'-piperidin]-1'-yl]-1-ethylpyridinium p-toluenesulfonate

**[0382]** The procedure of Example 23 was repeated by using the (-) form of the compound obtained in Example 35 and using ethyl p-toluenesulfonate instead of methyl p-toluenesulfonate to obtain the title compound.

IR (KBr) cm<sup>-1</sup>:3064, 1676, 1649, 1349, 1221, 1192, 1169, 1124, 1012

**[0383]** The procedures of Examples 36 and 52 can be repeated by using the (+) form obtained in Example 35 to thereby obtain the respective (+) bodies. Further, the procedures of Examples 37 and 38 - 49 can be repeated to obtain the respective (+) bodies.

(Example 53)

Synthesis of 1'-(4-amidinophenyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-1'-(4-cyanophenyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0384]** To a solution of the compound obtained in Example 1 <Step B-3> (50.0 mg) in 1,3-dimethyl-2-imidazolidone

(1 ml) were added 4-fluorobenzonitrile (18.9 mg) and diisopropylethylamine (20.2 mg). The mixture was heated under reflux at 150 °C to 160 °C for 4 hours. After allowing the reaction mixture to cool, water was added thereto and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 25:1) to obtain the title compound (25.0 mg).

NMR spectrum (CDCl<sub>3</sub>) δppm: 8.36(1H,s), 7.99-7.90(3H,m), 7.82-7.74(1H,m), 7.65-7.56(1H,m), 7.45(2H,d,J=9Hz), 6.81(2H,d,J=9Hz), 4.42-4.29(2H,m), 4.21(1H,d,J=12Hz), 3.67(1H,d,J=10Hz), 3.61(1H,d,J=10Hz), 3.43(3H,s), 3.50-3.16(5H,m), 3.21(1H,d,J=12Hz), 2.31(1H,d,J=12Hz), 2.08-1.80(2H,m), 1.58-1.46(2H,m)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-1'-(4-ethoxyimidoylphenyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0385]** The compound obtained in Step 1 (24.0 mg) was dissolved in 20% hydrochloric acid - ethanol solution (2 ml) and the solution was stirred at room temperature for 3 hours. Thereafter, the reaction mixture was concentrated under reduced pressure. To the resulting residue was added saturated aqueous solution of sodium hydrogencarbonate and the mixture was extracted with methylene chloride and the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 25:1) to obtain the title compound (16.8 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38-8.33(1H,m), 7.99-7.91(3H,m), 7.82-7.76(1H,m), 7.66-7.58(3H,m), 6.87-6.80(2H,m), 4.42-4.18(5H,m), 3.67(1H,d,J=10Hz), 3.61(1H,d,J=10Hz), 3.43(3H,s), 3.48-3.16(6H,m), 2.29(1H,d,J=12Hz), 2.08-1.84(2H,m), 1.58-1.50(2H,m), 1.44-1.36(3H,m)

<Step 3>

Synthesis of 1'-(4-amidinophenyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0386]** To a solution of the compound obtained in Step 2 (16.8 mg) in ethanol (2 ml) was added an excess of ammonium acetate and the mixture was heated under reflux at room temperature for 13 hours. After stirring, the reaction mixture was concentrated under reduced pressure. To the resulting residue was added saturated aqueous solution of sodium hydrogencarbonate and the mixture was extracted with methylene chloride. Thereafter, the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was suspended in methylene chloride and subjected to suction filtration. Thereafter, the filtrate was concentrated under reduced pressure to obtain the title compound (4.7 mg).

(Example 54)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridylmethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0387]** To a solution of the compound obtained in Example 1 <Step B-3> (50.0 mg) in methylene chloride (1.0 ml) were added 3A molecular sieves (15 mg), 4-pyridinecarboxyaldehyde (12.2 mg) and acetic acid (18.1 mg) and the mixture was stirred at room temperature for 30 minutes. Thereafter, sodium triacetoxo borohydride (55.1 mg) was added under cooling with ice. The mixture was stirred at room temperature for 8 hours. After adding 10% hydrochloric acid - methanol to the reaction mixture and stirring for 10 minutes, the reaction mixture was adjusted to pH 9 with saturated aqueous solution of sodium hydrogencarbonate. The insoluble content was removed by filtration, followed by extraction with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; methylene chloride : methanol = 400:1) to obtain the title compound (51.2 mg). HRMS: C<sub>28</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>5</sub> S(M<sup>+</sup>): Calculated: 570.1703, Found: 570.1716



(Example 55)

Synthesis of 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-2-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-1'-yl]pyridine 1-oxide

**[0388]** To a solution of the compound obtained in Example 1 <Step B-3> (50.0 mg) in ethanol (1 ml) were added 4-chloropyridine-N-oxide (16.2 mg) and diisopropylethylamine (26.9 mg) and the mixture was heated with stirring in a sealed tube at 150°C to 160°C for 18 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 10:1) to obtain the title compound (8.7 mg).

IR(KBr)cm<sup>-1</sup>:2925, 1658, 1506, 1346, 1165

(Example 56)

Synthesis of 1'-acetimidoyl-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0389]** To a solution of the compound obtained in Example 1 <Step B-3> (100 mg) in ethanol (4 ml) were added ethyl acetimidate hydrochloride (60.9 mg) and triethylamine (0.093 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 10:1) to obtain the title compound (97 mg).

IR (KBr) cm<sup>-1</sup>:3422, 2817, 1670, 1454, 1419, 1350, 1169

(Example 57)

Synthesis of 1'-acetimidoyl-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0390]** The procedure of Example 12 was repeated by using the compound obtained in Example 56 (40.0 mg) to obtain the title compound (43.7 mg).

(Example 58)

Synthesis of 6-(aminomethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(phthalimidoylmethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0391]** To a solution of phthalimide (4.88 g) and triphenylphosphine (8.69 g) in methylene chloride (150 ml) was added dropwise diethyl azodicarboxylate (40% toluene solution, 10.0 ml) under cooling with ice. Thereafter, the compound obtained in Example 3 <Step A-2> (3.0 g) was added and the mixture was stirred overnight at room temperature. After adding saturated aqueous solution of sodium hydrogencarbonate to the reaction mixture and extracting with methylene chloride, the organic layer was washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 19:1) to obtain the title compound (2.5 g). NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.44-8.41(1H,m), 8.25-8.18(2H,m), 8.00-7.75(8H,m), 7.62(1H,dd,J=2,9Hz), 6.65-6.51(2H,m), 4.58-4.51(1H,m), 4.39-4.24(2H,m), 4.19(1H,d,J=15Hz), 4.09(1H,d,J=15Hz), 3.44(1H,d,J=17Hz), 3.44-3.16(4H,m), 3.04(1H,d,J=12Hz), 2.45-2.38(1H,m), 1.89-1.62(2H,m), 1.47-1.40(2H,m)

<Step 2>

Synthesis of 6-(aminomethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0392]** To a suspension of the compound obtained in Step 1 (2.45 g) in ethanol (50 ml) was added hydrazine mono-

hydrate (0.37 ml) and the mixture was heated under reflux for 16 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 4:1) to obtain the title compound (1.432.5 g).  
 IR(KBr)cm<sup>-1</sup>:3395, 2920, 2360, 1666, 1597, 1348, 1167

(Example 59)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylaminomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0393]** To a solution of the compound obtained in Example 58 <Step 2> (50.0 mg) and triethylamine (0.02 ml) in methylene chloride (1 ml) was added ethyl chloroformate (12 mg) under cooling with ice and the mixture was stirred at room temperature for 2 days. After adding saturated aqueous solution of sodium hydrogencarbonate to the reaction mixture and extracting with methylene chloride, the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1) to obtain the title compound (49.4 mg).

IR(KBr)cm<sup>-1</sup>:3419, 2941, 1718, 1672, 1599, 1350, 1242, 1169

(Example 60)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethylaminomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0394]** To a solution of oxalyl dichloride (0.16 ml) in methylene chloride (7 ml) was gradually added dropwise a solution of dimethyl sulfoxide (0.29 ml) in methylene chloride (7 ml) at -75°C to -70°C. Thereafter, a solution of the compound obtained in Example 3 <Step A-2> (500 mg) in methylene chloride (7 ml) was gradually added thereto at the same temperature. After stirring the reaction mixture at -60°C to -50°C for 4 hours, triethylamine (0.77 ml) was added dropwise. The reaction mixture was warmed to room temperature and water was added. The mixture was extracted with methylene chloride. The organic layer was washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The amorphous content (450 mg) obtained by distilling off the solvent under reduced pressure was dissolved in methylene chloride (1.3 ml) and to the solution were added glycine ethyl ester hydrochloride (50.4 mg) and acetic acid (0.03 ml). Thereafter, sodium triacetoxy borohydride (127 mg) was added under cooling with ice and the mixture was stirred at room temperature for 8 hours. After adding saturated aqueous solution of sodium hydrogencarbonate to the reaction mixture and extracting with methylene chloride, the organic layer was washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 19:1) to obtain the title compound (17.8 mg).

IR(KBr)cm<sup>-1</sup>:3360, 2854, 1736, 1670, 1597, 1348, 1169

(Example 61)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(morpholinomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)-6-(p-toluenesulfonyloxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0395]** To a solution of the compound obtained in Example 3 <Step A-2> (200 mg) in methylene chloride (4 ml) were added triethylamine (0.146 ml) and p-toluenesulfonyl chloride (120 mg) under cooling with ice and the mixture was stirred overnight at room temperature. After adding saturated aqueous solution of sodium hydrogencarbonate to the reaction mixture and extracting with methylene chloride, the organic layer was washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 19:1) to obtain the title compound (234 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36-8.31(1H,m), 8.28-8.20(2H,m), 8.00-7.92(3H,m), 7.85-7.72(3H,m), 7.63(1H,dd,

J=2.9Hz), 7.44-7.37(2H,m), 6.68-6.63(2H,m), 4.31-4.17(5H,m), 3.64-3.37(3H,m), 3.34-3.17(3H,m), 2.49(3H,s), 2.32 (1H,d,J=12Hz), 2.10-1.98(1H,m), 1.94-1.81(1H,m), 1.58-1.43(2H,m)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(morpholinomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one

**[0396]** A solution of the compound obtained in Step 1 (171 mg) in morpholine (1.7 ml) was heated under reflux for 18 hours. After allowing the reaction mixture to cool, water was added thereto and the reaction mixture was extracted with methylene chloride. The organic layer was washed with water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; n-hexane : ethyl acetate = 1:1 - 1:2) to obtain the title compound (88.8 mg).

IR(KBr)cm<sup>-1</sup>:2951, 2852, 1670, 1597, 1350, 1167

(Example 62)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(morpholinomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one dimethanesulfonate

**[0397]** The procedure of Example 12 was repeated by using the compound obtained in Example 61 <Step 2> (50.9 mg) to obtain the title compound (50.8 mg).

(Example 63)

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-1'-(2-chloropyrimidin-4-yl)-7-oxaspiro [bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0398]** To a suspension of the compound obtained in Example 7 <Step B-1> (300 mg) and 2,4-dichloropyrimidine (88 mg) in isoamyl alcohol (4 ml) was added sodium hydrogencarbonate (174 mg) and the mixture was stirred at 70°C for 1.5 hours. After allowing the reaction mixture to cool, water was added and the reaction mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride: methanol = 125:1 - 100:1) to obtain the title compound (237 mg).

(Example 64)

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(2-naphthalenesulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0399]** The compound obtained in Example 63 (110 mg) was dissolved in ethanol (6 ml) and to the solution was added 5% palladium- barium carbonate (1.65 g). The mixture was stirred at room temperature for 15 hours under a hydrogen atmosphere. The reaction mixture was filtered through Celite. The solvent was distilled off under reduced pressure and the resulting residue was purified by thin-layer chromatography (developer; n-hexane : acetone = 1:1) to obtain the title compound (5.5 mg).

HRMS:C<sub>27</sub>H<sub>29</sub>N<sub>5</sub>O<sub>6</sub> S(M<sup>+</sup>): Calculated: 551.1838, Found: 551.1804

(Example 65)

Synthesis of 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one

**[0400]** To a suspension of the compound obtained in Example 7 <Step B-1> (100mg) and sodium hydrogencarbonate (49.6 mg) in isoamyl alcohol (5 ml) was added 4-chloropyrimidine hydrochloride (29.7 mg) synthesized by the procedure described in WO98/21188. The mixture was stirred at 80°C for 4 hours. The reaction mixture was allowed to cool and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent;

methylene chloride : methanol = 19:1) to obtain the title compound (37.0 mg).  
 HRMS:  $C_{27}H_{28}ClN_5O_6$  S(M<sup>+</sup>): Calculated: 585.1448, Found: 585.1497

(Example 66)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

**[0401]** Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-1'-[2-(methylthio)pyrimidin-4-yl]-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0402]** The procedure of Example 2 <Step 1> was repeated by using the compound obtained in Example 7 <Step B-1> (930 mg) to obtain the title compound (480 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.41-8.34(1H,m), 8.04-7.89(4H,m), 7.79(1H,dd,J=2,9Hz), 7.62(1H,dd,J=2,9Hz), 6.17(1H,d,J=6Hz), 4.50-4.32(2H,m), 4.25(1H,d,J=12Hz), 4.01-3.30(6H,m), 3.38(1H,d,J=17Hz), 3.20(1H,d,J=12Hz), 2.76-2.60(1H,m), 2.45(3H,s), 2.33(1H,d,J=12Hz), 2.00-1.67(2H,m), 1.56-1.36(2H,m)

**[0403]** At that time, 6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-1'-[2-(methylthio)pyrimidin-4-yl]-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one (228 mg) was also obtained.

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.38(1H,s), 8.01(1H,d,J=6Hz), 8.01-7.90(3H,m), 7.84-7.78(1H,m), 7.66-7.60(1H,m), 6.16(1H,d,J=6Hz), 4.51(1H,d,J=12Hz), 4.48-4.32(2H,m), 4.26(1H,d,J=12Hz), 4.18(1H,d,J=12Hz), 4.00-3.80(2H,m), 3.51-3.30(2H,m), 3.37(1H,d,J=17Hz), 3.18(1H,d,J=12Hz), 2.46(3H,s), 2.36(1H,d,J=12Hz), 2.14(3H,s), 1.97-1.40(4H,m)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0404]** The procedure of Example 2 <Step 2> was repeated by using the compound obtained in <Step 1> (300 mg) to obtain the title compound (197 mg).

IR(KBr)cm<sup>-1</sup>: 3400, 1666, 1595, 1348, 1169

(Example 67)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-1'-[2-(methylthio)pyrimidin-4-yl]-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0405]** The procedure of Example 2 <Step 1> was repeated by using the compound obtained in Example 25 <Step 3> (390 mg) to obtain the title compound (363 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36(1H,s), 8.02(1H,d,J=6Hz), 7.99-7.92(3H,m), 7.81-7.75(1H,m), 7.65-7.59(1H,m), 6.18(1H,d,J=6Hz), 4.77 (1H,d,J=11Hz), 4.38-4.22(3H,m), 4.10(1H,d,J=12Hz), 4.00-3.80(2H,m), 3.58-3.34 (3H,m), 3.35(1H,d,J=17Hz), 2.53-2.43(1H,m), 2.47(3H,s), 1.83-1.51(4H,m), 1.36(3H,t,J=7Hz)

<Step 2>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0406]** The procedure of Example 2 <Step 2> was repeated by using the compound obtained in Step 1 (360 mg) to obtain the title compound (41 mg).

HRMS:  $C_{27}H_{28}ClN_5O_6$  S(M<sup>+</sup>): Calculated: 585.1448, Found: 585.1456

(Example 68)

Synthesis of 1,4-diaza-6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0407]** The procedure of Example 27 was repeated by using the compound obtained in Example 67 <Step 2> (10 mg) to obtain the title compound (1.9 mg).

IR(KBr)cm<sup>-1</sup>: 3400, 1657, 1599, 1346, 1169

(Example 69)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of ethyl 2-[(6-chloronaphthalen-2-ylsulfonyl)(2-oxopropan-1-yl)amino]acetate

**[0408]** The procedure of Example 1 <Step A-2> was repeated by using the compound obtained in Example 1 <Step A-1> (1.0 g) and using chloroacetone (0.368 ml) instead of 1-acetoxy-3-chloroacetone to obtain the title compound (1.08 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.40-8.38(1H,m), 7.93-7.86(3H,m), 7.83-7.78(1H,m), 7.56(1H,dd,J=2,9Hz), 4.29(2H,s), 4.17(2H,s), 4.04(2H,q,J=7Hz), 2.19(3H,s), 1.16(3H,t,J=7Hz)

<Step 2>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0409]** The procedure of Example 1 <Step A-3> was repeated by using the compound obtained in Step 1 (870 mg) to obtain the title compound (150 mg).

NMR spectrum (CDCl<sub>3</sub>) δppm: 8.33(1H,s), 7.97-7.88(3H,m), 7.80-7.73(1H,m), 7.60(1H,dd,J=2,9Hz), 7.34-7.18(5H,m), 4.37-4.26(1H,m), 4.25-4.08(2H,m), 3.46(2H,s), 3.32-3.22(1H,m), 3.04(1H,d,J=12Hz), 2.65-2.20(4H,m), 2.33(1H,d,J=11Hz), 1.90-1.73(2H,m), 1.59(3H,s), 1.47-1.37 (2H,m)

<Step 3>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0410]** The procedure of Example 7 <Step B-1> was repeated by using the compound obtained in Step 2 (195 mg) to obtain the title compound (142 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.36-8.33(1H,m), 7.97-7.92(3H,m), 7.80-7.76(1H,m), 7.61(1H,dd,J=2,9Hz), 4.38-4.29(1H,m), 4.24(1H,d,J=12Hz), 4.14(1H,d,J=11Hz), 3.32-3.23(1H,m), 3.08-2.98(1H,m), 3.04(1H,d,J=12Hz), 2.92-2.82(1H,m), 2.78-2.61(2H,m), 2.34(1H,d,J=11Hz), 1.85-1.69(2H,m), 1.61(3H,s), 1.44-1.27(2H,m)

<Step 4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0411]** The procedure of Example 20 <Step 5> was repeated by using the compound obtained in Step 3 (130 mg) to obtain the title compound (95 mg).

HRMS:C<sub>26</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>4</sub> S(M<sup>+</sup>): Calculated: 526.1441, Found: 526.1408

(Example 70)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfonate

**[0412]** The procedure of Example 12 was repeated by using the compound obtained in Example 69 <Step 4> (35.0 mg) to obtain the title compound (37.9 mg).

(Example 71)

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(3-methoxycarbonylpropyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of ethyl 2-[(5-methoxycarbonyl-2-oxopentane-1-yl)(6-chloronaphthalen-2-ylsulfonyl)amino]acetate

**[0413]** The procedure of Example 1 <Step A-2> was repeated by using methyl 6-bromo-5-oxohexanoate (10.8 g) to obtain the title compound (11.4 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.39(1H,s), 7.95-7.84(3H,m), 7.84-7.77(1H,m), 7.60-7.52(1H,m), 4.27(2H,s), 4.17(2H,s), 4.04(2H,q,J=7Hz), 3.66(3H,s), 2.55(2H,t,J=7Hz), 2.31(2H,t,J=7Hz), 1.96-1.83(2H,m), 1.15(3H,t,J=7Hz)

<Step 2>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(3-methoxycarbonylpropyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0414]** The procedure of Example 1 <Step C-1> was repeated by using the compound obtained in Step 1 (5.56 g). The thus obtained compound was used as the starting material to synthesize according to the procedure of Example 1 <Step C-2> to thereby obtain the title compound (1.50 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.39-8.31(1H,m), 8.00-7.87(3H,m), 7.78(1H,dd,J=2,9Hz), 7.60(1H,dd,J=2,9Hz), 7.36-7.17(5H,m), 4.39-4.13(3H,m), 3.69(3H,s), 3.47(2H,s), 3.30(1H,d,J=17Hz), 3.04(1H,d,J=12Hz), 2.67-2.12(6H,m), 2.22(1H,d,J=12Hz), 2.12-1.53(6H,m), 1.53-1.30(2H,m)

<Step 3>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(3-methoxycarbonylpropyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0415]** The procedure of Example 7 <Step B-1> was repeated by using the compound obtained in Step 2 (0.53 g) to obtain the title compound (0.30 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.35(1H,s), 8.02-7.92(3H,m), 7.83-7.74(1H,m), 7.61(1H,dd,J=2,9Hz), 4.40-4.17(3H,m), 3.70(3H,s), 3.31(1H,d,J=17Hz), 3.11-2.97(1H,m), 3.04(1H,d,J=12Hz), 2.97-2.79(1H,m), 2.79-2.68(2H,m), 2.48-2.30(2H,m), 2.24(1H,d,J=12Hz), 2.12-1.67(6H,m), 1.45-1.30(2H,m)

<Step 4>

Synthesis of 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(3-methoxycarbonylpropyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0416]** The procedure of Example 20 <Step 5> was repeated by using the compound obtained in Step 3 (420 mg) to obtain the title compound (90 mg).

IR(KBr)cm<sup>-1</sup>: 3442, 2949, 1732, 1666, 1597, 1348, 1167

(Example 72)

Synthesis of ammonium 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-6-yl]butylate

**[0417]** The procedure of Example 50 was repeated by using the compound obtained in Example 71 <Step 4> (90 mg) to obtain the title compound (70 mg).

IR(KBr)cm<sup>-1</sup>: 3945, 2949, 1666, 1599, 1348, 1167

(Example 73)

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-1'-(4-pyridyl)Spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 6-(acetoxymethyl)-1,4,7-triaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0418]** The procedure of Example 1 <Step A-3> was repeated by using the compound obtained in Example 1 <Step A-2> (10.3 g) and 4-amino-4-(aminomethyl)-1-benzylpiperidine (5.26 g) to obtain the title compound (7.76 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.37-8.32(1H,m), 7.97-7.89(3H,m), 7.80-7.74(1H,m), 7.59(1H,dd,J=2,9Hz), 7.35-7.17(5H,m), 4.36-4.12(5H,m), 3.45(2H,s), 3.33(1H,d,J=17Hz), 2.88(1H,d,J=12Hz), 2.63-2.40(2H,m), 2.31(1H,d,J=12Hz), 2.37-1.93(2H,m), 2.11(3H,s), 1.80-1.65(2H,m), 1.40-1.25(2H,m)

<Step 2>

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0419]** To a solution of the compound obtained in Step 1 (5.00g) and 1,8-bis(N,N-dimethylamino)naphthalene (2.15 g) in 1,2-dichloroethane (50 ml) was added 1-chloroethyl chloroformate (2.28 ml) under cooling with ice. The mixture was stirred at room temperature for 30 minutes and then heated under reflux for 2 hours. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. To the residue was added methanol (50 ml) and the mixture was heated under reflux for 1 hour. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. The resulting residue was crystallized by addition of diethyl ether. The supernatant was removed by decantation and the solvent was distilled off under reduced pressure. The resulting residue was dissolved in methanol (50 ml) and to the solution was added 1N aqueous solution of sodium hydroxide (33.5 ml) at room temperature. The mixture was stirred at room temperature for 1 hour. The precipitated crystals were collected by filtration and washed with methylene chloride to obtain the title compound (3.30 g).

NMR spectrum (\*DMSO-d<sub>6</sub>) δppm: 8.60-8.55(1H,m), 8.30(1H,d,J=9Hz), 8.27-8.24(1H,m), 8.17(1H,d,J=9Hz), 7.87(1H,dd,J=2,9Hz), 7.73(1H,dd,J=2,9Hz), 5.26-5.18(1H,m), 4.01(1H,d,J=17Hz), 4.00-3.89(2H,m), 3.58-3.30(3H,m), 2.78(1H,d,J=11Hz), 2.85-2.25(4H,m), 2.36(1H,d,J=12Hz), 1.99(1H,brs), 1.60-1.44(2H,m), 1.20-1.04(2H,m)

<Step 3>

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0420]** The procedure of Example 20 <Step 5> was repeated by using the compound obtained in Step 2 (3.30 g) to obtain the title compound (2.50 g).

IR(KBr) cm<sup>-1</sup>: 3336, 2939, 1657, 1601, 1454, 1421, 1346, 1167

(Example 74)

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0421]** To a solution of the compound obtained in Example 73 <Step 3> (1.00 g) in methylene chloride (10 ml) were added acetic acid (0.42 ml) and paraformaldehyde (0.12 g) at room temperature. After stirring the mixture for 30 minutes, sodium triacetoxy borohydride (1.56 g) was added thereto. The mixture was stirred at room temperature for 6 days and thereafter heated under reflux for 8 hours. After addition of water, the reaction mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography [ChromatorexNH™(eluent; methylene chloride - 1% methanol / methylene chloride) to obtain the title compound (0.45g).

IR(KBr)cm<sup>-1</sup>:3444, 2943, 1657, 1599, 1456, 1348, 1167

(Example 75)

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0422]** The procedure of Example 1 <Step A-5> was repeated by using the compound obtained in Example 7466 (0.34 g) to obtain the title compound (0.14 g).

IR(KBr)cm<sup>-1</sup>:3446, 2930, 1662, 1597, 1454, 1348, 1167

(Example 76)

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one dimethanesulfonate

**[0423]** The procedure of Example 12 was repeated by using the compound obtained in Example 75 (0.13 g) to obtain the title compound (0.17 g).

(Example 77)

Synthesis of 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)-spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0424]** The procedure of Example 1 <Step A-5> was repeated by using the compound obtained in Example 73 <Step 3> (1.50 g) to obtain the title compound (0.75 g).

IR(KBr)cm<sup>-1</sup>:3435, 2939, 1662, 1597, 1454, 1421, 1350, 1167

(Example 78)

Synthesis of 7-acetyl-1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

<Step 1>

Synthesis of 1,4,7-triaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0425]** The procedure of Example 1 <Step A-4> was repeated by using the compound obtained in Example 73 <Step 1> (2.00 g) to obtain the title compound (1.75 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.35-8.32(1H,m), 7.96-7.88(3H,m), 7.80-7.73(1H,m), 7.60(1H,dd,J=2,9Hz), 7.34-7.19(5H,m), 4.37-4.20(2H,m), 4.17-4.08(1H,m), 4.00-3.93(1H,m), 3.55-3.47(1H,m), 3.46(2H,s), 3.32(1H,d,J=17Hz), 2.93(1H,d,J=12Hz), 2.64-2.40(2H,m), 2.35-2.15(2H,m), 2.25(1H,d,J=12Hz), 1.80-1.71(2H,m), 1.44-1.35(2H,m)



<Step 2>

Synthesis of 1,4,7-triaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0426]** The procedure of Example 1 <Step A-5> was repeated by using the compound obtained in Step 1 (1.72 g) to obtain the title compound (1.43 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.35-8.31(1H,m), 7.97-7.88(3H,m), 7.80-7.74(1H,m), 7.59(1H,dd,J=2,9Hz), 7.34-7.19(5H,m), 4.31(1H,d,J=17Hz), 4.22-4.08(2H,m), 3.70(1H,d,J=10Hz), 3.49-3.38(1H,m), 3.45(2H,s), 3.42(3H,s), 3.27(1H,d,J=17Hz), 2.88(1H,d,J=12Hz), 2.60-2.40(2H,m), 2.31-2.10(2H,m), 2.21(1H,d,J=12Hz), 1.80-1.65(2H,m), 1.40-1.21(2H,m)

<Step 3>

Synthesis of 7-acetyl-1,4,7-triaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0427]** To a solution of the compound obtained in Step 2 (0.30 g) and triethylamine (0.11 ml) in methylene chloride (3 ml) was added acetyl chloride (56 µl) under cooling with ice and the mixture was stirred at room temperature for 2 hours. After addition of saturated aqueous solution of sodium hydrogencarbonate, the reaction mixture was extracted with methylene chloride and the organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; ethyl acetate : methanol = 19:1) to obtain the title compound (0.31 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.35-8.31(1H,m), 7.98-7.88(3H,m), 7.77(1H,dd,J=2,9Hz), 7.59(1H,dd,J=2,9Hz), 7.35-7.20(5H,m), 5.16(1H,d,J=13Hz), 4.54(1H,d,J=11Hz), 4.42(1H,d,J=17Hz), 4.37-4.29(1H,m), 3.90-3.83(1H,m), 3.47(2H,s), 3.37-3.25(2H,m), 3.32(3H,s), 2.94-2.75(2H,m), 2.55-2.25(2H,m), 2.29(1H,d,J=13Hz), 2.28(3H,s), 2.18-2.00(2H,m), 1.95-1.80(1H,m), 1.28-1.13(1H,m)

<Step 4>

Synthesis of 7-acetyl-1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0428]** To a solution of the compound obtained in Step 3 (0.28 g) and 1,8-bis(N,N-dimethylamino)naphthalene (20 mg) in 1,2-dichloroethane (3 ml) was added 1-chloroethyl chloroformate (0.13 ml) under cooling with ice and the mixture was stirred at room temperature for 1 hour. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. To the residue was added methanol (3 ml) and the mixture was heated under reflux for 1 hour. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. To the resulting residue was added water and the mixture was washed with diethyl ether. The aqueous layer was adjusted to pH 10 with potassium carbonate and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; methylene chloride - 2% methanol/methylene chloride) to obtain the title compound (0.15 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.34(1H,s), 8.00-7.88(3H,m), 7.81-7.74(1H,m), 7.60(1H,dd,J=2,9Hz), 5.16(1H,d,J=12Hz), 4.61(1H,d,J=11Hz), 4.42(1H,d,J=17Hz), 4.34(1H,d,J=10Hz), 3.87(1H,d,J=10Hz), 3.40-3.27(2H,m), 3.34(3H,s), 3.15-2.97(2H,m), 2.80-2.65(1H,m), 2.55-2.44(1H,m), 2.43-2.23(2H,m), 2.28(3H,s), 2.03-1.85(2H,m), 1.30-1.17(1H,m)

<Step 5>

Synthesis of 7-acetyl-1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0429]** The procedure of Example 20 <Step 5> was repeated by using the compound obtained in Step 4 (110 mg) to obtain the title compound (78 mg).

IR(KBr)cm<sup>-1</sup>: 3435, 2920, 1666, 1639, 1597, 1383, 1346, 1167

(Example 79)

Synthesis of 1,4,7-triaza-4-(2-naphthalenesulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0430]** To a solution of the compound obtained in Example 77 (200 mg) in methanol (4 ml) were added 1N hydrochloric acid (1.8 ml), then 10% palladium-active carbon (40 mg). The mixture was stirred at room temperature for 4 days under a hydrogen atmosphere. The reaction mixture was filtered through Celite and thereafter concentrated under reduced pressure. The resulting residue was adjusted to pH 10 with aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; methylene chloride - methylene chloride : methanol = 199:1) to obtain the title compound (140 mg).

(Example 80)

Synthesis of 1,4,7-triaza-4-(2-naphthalenesulfonyl)-6-(methoxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0431]** The procedure of Example 79 was repeated by using the compound obtained in Example 75 (130 mg) to obtain the title compound (69.0 mg).

(Example 81)

Synthesis of (+)-1,4-diaza-6-(methoxymethyl)-4-(2-naphthalenesulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0432]** The procedure of Example 79 was repeated by using (+)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one (100 mg) to obtain the title compound (90.7 mg).

(Example 82)

Synthesis of (-)-1,4-diaza-6-(methoxymethyl)-4-(2-naphthalenesulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0433]** The procedure of Example 79 was repeated by using (-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one (100 mg) to obtain the title compound (84.1 mg).

Synthesis examples of the intermediate compounds of the present invention are described below as Reference Examples.

(Reference Example 1)

<Step 1>

Synthesis of ethyl 2-[(2-nitrobenzenesulfonyl)amino]acetate

**[0434]** To a suspension of glycine ethyl ester hydrochloride (9.45 g) in methylene chloride (100 ml) were added triethylamine (18.9 ml) and 2-nitrobenzenesulfonyl chloride (10.0 g) in succession under cooling with ice and the mixture was stirred at room temperature for 2 days. To the reaction mixture was added 1N hydrochloric acid under cooling with ice, followed by extraction with methylene chloride. The organic layer was washed with saturated aqueous solution of sodium hydrogencarbonate, then saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the precipitated crystals were washed with a mixed solvent of n-hexane and diethyl ether, collected by filtration and air-dried to obtain the title compound (10.8 g).  
NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.14-8.06(1H,m), 7.98-7.91(1H,m), 7.80-7.71(2H,m), 6.06(1H,brs), 4.06(2H,q,J=7Hz), 4.01(2H,s), 1.20-1.13(3H,m)

<Step 2>

Synthesis of ethyl 2-[(3-acetoxy-2-oxopropan-1-yl)(2-nitrobenzenesulfonyl)amino]acetate

**[0435]** To a suspension of the compound obtained in Step 1 (10.0 g), potassium carbonate (7.20 g) and sodium iodide (5.2 g) in N,N-dimethylformamide (100 ml) was added a solution (20 ml) of 1-acetoxy-3-chloroacetone (7.84 g) in N,N-dimethylformamide under cooling with ice and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture under cooling with ice, followed by extraction with ethyl acetate. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. To the resulting residue was added hexane and the mixture was stirred. The supernatant was removed by decantation and crystallized by addition of diethyl ether. The crystals were collected by filtration and air-dried to thereby obtain the title compound (9.36 g).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.10-8.02(1H,m), 7.76-7.62(3H,m), 4.73(2H,s), 4.53(2H,s), 4.24(2H,s), 4.15(2H,q, J=7Hz), 2.16(3H,s), 1.24(3H,t, J=7Hz)

<Step 3>

Synthesis of ethyl 2-[(3-acetoxy-2-oxopropan-1-yl)(benzyloxycarbonyl)amino]acetate

**[0436]** To a solution of the compound obtained in Step 21 (5.0 g) in acetonitrile (75 ml) were added thiophenol (1.40 ml) and cesium carbonate (12.1 g) under cooling with ice. The mixture was stirred at room temperature for 1 hour. After further adding thiophenol (1.0 ml) and stirring at room temperature, the reaction mixture was filtered through Celite. After washing the Celite with methylene chloride (500 ml), to the filtrate were added triethylamine (5.20 ml), then benzyl chloroformate (4.68 ml) under cooling with ice. The mixture was stirred overnight at room temperature. After addition of water, the reaction mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; n-hexane : ethyl acetate = 20:1 - 2:1) to obtain the title compound (1.41 g).

NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.38-7.24(5H,m), 5.08(2H,s), 4.75(2H,s), 4.25(2H,s), 4.10(2H,q, J=7Hz), 4.03(2H,s), 2.07(3H,s), 1.17(3H,t, J=7Hz)

<Step 4>

Synthesis of ethyl 2-[[2-(acetoxymethyl)-3,8-diaza-8benzyl-1-oxaspiro[bicyclo[4.5]decan-2-yl]methyl] (benzyloxycarbonyl)amino]acetate

**[0437]** To a solution of the compound obtained in Step 3 (1.0 g) and 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine (879 mg) in methylene chloride (50 ml) were added acetic acid (0.1 ml) and 3A molecular sieves (2.0g). The mixture was heated under reflux for 2 hours. The reaction mixture was allowed to cool and purified by silica gel column chromatography (eluent; methylene chloride : methanol = 100:0 - 50:1 - 20:1) to obtain the title compound quantitatively. NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.37-7.16(10H,m), 5.07(2H,s), 4.21-3.88(6H,m), 3.54-3.34(2H,m), 3.44(2H,s), 3.30-3.20(1H,m), 2.90-2.76(2H,m), 2.52-2.38(2H,m), 2.34-2.22(2H,m), 1.94(3H,s), 1.65-1.45(4H,m), 1.16(3H,t, J=7Hz)

<Step 5>

Synthesis of 6-(acetoxymethyl)-1,4-diaza-1'-benzyl-4-benzyloxycarbonyl-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0438]** The solution of the compound obtained in Step 43 (1.60 g) in toluene (32 ml) was stirred in a sealed tube at 180°C for 2 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; methylene chloride : methanol = 50:1 - 20:1) to obtain the title compound (890 mg).

NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.38-7.16(10H,m), 5.11(2H,s), 4.38(1H,d, J=13Hz), 4.30-3.99(4H,m), 3.82(1H,d, J=18Hz), 3.47(2H,s), 3.09(1H,d, J=11Hz), 3.00(1H,d, J=13Hz), 2.58-2.22(4H,m), 1.94(3H,s), 1.80-1.72(2H,m), 1.56-1.50(2H,m)

<Step 6>

Synthesis of 1,4-diaza-1'-benzyl-4-(benzyloxycarbonyl)-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0439]** To a solution of the compound obtained in Step 5 (400 mg) in ethanol (8 ml) was added hydrazine monohydrate (0.38 ml) under cooling with ice. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the resulting residue was purified by silica gel chromatography (eluent; methylene chloride : methanol = 50:1 - 25:1) to obtain the title compound (329 mg).

NMR spectrum (\*DMSO- $d_6$ , 100°C)  $\delta$ ppm: 7.38-7.16(10H,m), 5.10(2H,s), 4.76-4.67(1H,m), 4.29(1H,d,J=13Hz), 4.17(1H,d,J=18Hz), 4.10(1H,d, J=11Hz), 3.81(1H,d,J=18Hz), 3.47(2H,s), 3.44-3.35(2H,m), 3.09(1H,d,J=11Hz), 2.99-2.91(1H,m), 2.59-2.42(2H,m), 2.37-2.24(2H,m), 1.86-1.72(2H,m), 1.58-1.42(2H,m)

<Step 7>

Synthesis of 1,4-diaza-4-(benzyloxycarbonyl)-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0440]** To a solution of the compound obtained in Step 6 (100 mg) and 1,8-bis(N,N-dimethylamino)naphthalene (9.2 mg) in 1,2-dichloroethane (3 ml) was added 1-chloroethyl chloroformate (58  $\mu$ l) under cooling with ice and the mixture was stirred at room temperature for 1 hour. Then, methanol (3 ml) was added to the reaction mixture and the mixture was heated with stirring at an ambient temperature of 70°C. The reaction mixture was allowed to cool and concentrated. To the residue was added 1N hydrochloric acid and benzyl chloride was extracted with diethyl ether. The diethyl ether layer was further extracted with 1N hydrochloric acid and combined with the above aqueous layer. The aqueous layer was adjusted to pH 9 with sodium carbonate under cooling with ice and extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography [Chromatorex NH<sup>TM</sup>] (eluent; methylene chloride : methanol = 50:1 - 25:1) to obtain the title compound quantitatively.

NMR spectrum (\*DMSO- $d_6$ , 100°C)  $\delta$ ppm: 7.38-7.26(5H,m), 5.11(2H,s), 4.69(1H,brs), 4.30(1H,d,J=13Hz), 4.18(1H,d,J=18Hz), 4.12(1H,d,J=11Hz), 3.81(1H,d,J=18Hz), 3.40(2H,s), 3.06(1H,d,J=11Hz), 2.94(1H,d,J=13Hz), 3.02-2.74(2H,m), 2.62-2.50(2H,m), 1.72-1.66(2H,m), 1.44-1.36(2H,m)

<Step 8>

Synthesis of 1,4-diaza-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0441]** To a solution of the compound obtained in Step 7 (4.5 mg) in methanol (1 ml) was added 10% palladium-active carbon (2 mg) and the mixture was stirred at room temperature for 2 hours under a hydrogen atmosphere. The reaction mixture was filtered through Celite and washed with methanol. The filtrate was concentrated to obtain the title compound quantitatively.

NMR spectrum (\*CDCl<sub>3</sub>)  $\delta$ ppm: 4.42(1H,d,J=12Hz), 3.77-3.58(4H,m), 3.50(1H,d,J=18Hz), 3.05(1H,d,J=12Hz), 3.10-2.94(2H,m), 2.82-2.70(2H,m), 2.67(1H,d,J=12Hz), 1.90-1.46(4H,m)

(Reference Example 2)

<Step 1>

Synthesis of 1,4-diaza-1'-benzyl-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0442]** To a solution of the compound obtained in Reference Example 1 <Step 6> (25.0 mg) in acetonitrile (1 ml) was added trimethylsilane iodide (20  $\mu$ l) under cooling with ice. The mixture was stirred under cooling with ice for 30 minutes, then at room temperature for 3 days. Trimethylsilane iodide (0.2 ml) was further added and the mixture was stirred overnight at room temperature. To the reaction mixture was added 1N hydrochloric acid under cooling with ice and benzyl iodide was extracted with diethyl ether. The organic layer was extracted with 1N hydrochloric acid and combined with the previous aqueous layer. After adjusting to pH 9 with sodium carbonate, the aqueous layer was concentrated. To the resulting residue was added methylene chloride and the insoluble content was removed by filtration and the filtrate was washed with methylene chloride and concentrated to obtain the title compound (18.3 mg).

NMR spectrum (\*CDCl<sub>3</sub>)  $\delta$ ppm: 7.36-7.22(5H,m), 4.37(1H,d,J=12Hz), 3.76-3.42(5H,m), 3.51(2H,s), 3.05(1H,d,

J=12Hz), 2.70-2.48(3H,m), 2.46-2.29(2H,m), 1.94-1.73(2H,m), 1.70-1.50(2H,m)

<Step 2>

- 5 Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

[0443] To a solution of the compound obtained in Step 1 (13.5 mg) and triethylamine (9  $\mu$ l) in methylene chloride (0.5 ml) was added 6-chloronaphthalene-2-sulfonyl chloride (12 mg) under cooling with ice and the mixture was stirred at room temperature for 5 days. After addition of water under cooling with ice, the reaction mixture was extracted with methylene chloride. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was purified by preparative thin-layer chromatography (developer; methylene chloride : methanol = 20:1) to obtain the title compound (2.8 mg).

(Reference Example 3)

<Step 1>

- 20 Synthesis of ethyl 2-[(benzyloxycarbonyl)(2,2-diethoxyethyl)amino]acetate

[0444] To aminoacetaldehyde diethyl acetal (43.6 ml) was added dropwise ethyl bromoacetate (34.5 ml) under cooling with ice and N,N-dimethylformamide (150 ml), cesium carbonate (97.7 g) and sodium iodide (4.5 g) were added. The mixture was stirred overnight at room temperature. The reaction mixture was poured into ice water, adjusted to pH 1 with hydrochloric acid and extracted with ethyl acetate. The aqueous layer was adjusted to pH 10 with sodium carbonate and extracted with methylene chloride. Thereafter, the organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the resulting residue was dissolved in methylene chloride (200 ml) and triethylamine (16.1 ml) was added. Thereafter, a solution of benzyl chloroformate (16.5 ml) in methylene chloride (20 ml) was added dropwise over 30 minutes under cooling with ice. The reaction mixture was stirred under cooling with ice for 30 minutes, then at room temperature for 1 hour, and thereafter extracted with 1N hydrochloric acid. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent; n-hexane : diethyl ether = 2:1 - 1:1) to obtain the title compound (28.9 g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 7.42-7.25(5H,m), 5.24-5.08(2H,m), 4.62-4.44(1H,m), 4.23-4.07(4H,m), 3.78-3.36(6H,m), 1.30-1.11(9H,m)

<Step 2>

Synthesis of ethyl 2-[(benzyloxycarbonyl)(formylmethyl)amino]acetate

[0445] After adding water (60 ml) to a solution of the compound obtained in Step 1 (14.1 g) in chloroform (120 ml), trifluoroacetic acid (153 ml) was added dropwise over 2 hours under cooling with ice. The mixture was stirred under cooling with ice for 1 hour and at room temperature for 1.5 hours. After adding water to the reaction mixture and extracting with methylene chloride, the organic layer was washed with aqueous solution of 10% potassium carbonate, water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off under reduced pressure to obtain the title compound (10.3g).

NMR spectrum ( $^1\text{H}$  NMR,  $\text{CDCl}_3$ )  $\delta$ ppm: 9.70-9.56(1H,m), 7.40-7.26(5H,m), 5.23-5.11(2H,m), 4.25-4.01(6H,m), 1.32-1.18(3H,m)

<Step 3>

Synthesis of 2-[[[3,8-diaza-8-benzyl-1-oxaspiro[4.3.0]decan-2-yl)methyl](benzyloxycarbonyl)amino]acetic acid

[0446] To a solution of the compound obtained in Step 2 (1.35 g) in methanol (25 ml), was added a solution of lithium hydroxide monohydrate (0.24 g) in water (10 ml) under cooling with ice. The mixture was stirred under cooling with ice for 10 minutes and at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure and to the resulting residue was added water, followed by extraction with ethyl acetate. The aqueous layer was adjusted to pH 2 with 6N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and

saturated sodium chloride solution and dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off under reduced pressure to obtain a compound. To a solution of this compound (1.21 g) in methylene chloride (40 ml) were added toluene (40 ml), 4-(aminomethyl)-1-benzyl-4-hydroxypiperidine (1.06 g) and magnesium sulfate (2.90 g) and the mixture was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was solidified by addition of diethyl ether and thereafter the solid content was collected by filtration and dried in vacuum to thereby obtain the title compound (2.05 g).

NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.39-7.15(10H,m), 5.15-4.98(2H,m), 4.62-4.57(1H,m), 4.13-3.91(2H,m), 3.67-3.25(4H,m), 2.88-2.60(2H,m), 2.56-2.26(4H,m), 1.65-1.33(4H,m)

<Step 4>

Synthesis of 1,4-diaza-1'-benzyl-4-(benzyloxycarbonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0447]** To a solution of the compound obtained in Step 3 (1.61 g) in methylene chloride (30 ml) was added dicyclohexylcarbodiimide (0.81 g) under cooling with ice. The mixture was stirred for 30 minutes under cooling with ice and overnight at room temperature. Thereafter, the insoluble content was removed by filtration. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent; ethyl acetate : methanol = 9:1) to obtain the title compound (0.63 g).

NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.40-7.15(10H,m), 5.12(2H,s), 5.00(1H,dd,J=4,9Hz), 4.35-4.27(1H,m), 4.21(1H,d,J=18Hz), 3.76(1H,d,J=18Hz), 3.70(1H,d,J=11Hz), 3.48(2H,s), 3.10(1H,d,J=11Hz), 3.00-2.88(1H,m), 2.57-2.32(4H,m), 1.84-1.55(4H,m)

<Step 5>

Synthesis of 1,4-diaza-4-(benzyloxycarbonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0448]** The procedure of Reference Example 1 <Step 7> was repeated by using the compound obtained in Step 4 (1.00 g) to obtain the title compound (0.57 g).

NMR spectrum (\*DMSO-d<sub>6</sub>, 100°C) δppm: 7.38-7.27(5H,m), 5.12(2H,s), 5.01(1H,dd,J=4,9Hz), 4.36-4.27(1H,m), 4.26-4.17(1H,m), 3.81-3.65(2H,m), 3.12-3.06(1H,m), 2.98-2.74(3H,m), 2.64-2.54(2H,m), 1.67-1.60(2H,m), 1.55-1.47(2H,m)

<Step 6>

Synthesis of 1,4-diaza-4-(benzyloxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0449]** To a solution of the compound obtained in Step 5 (0.1 g) and 4-chloropyridine (0.33 g) in ethanol (2.9 ml) was added N-ethyl-diisopropylamine (56 μl). The mixture was heated with stirring in a sealed tube at 150 - 160°C. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; ethyl acetate : methanol = 98:2 - 95:5). The fraction containing the compound of interest was concentrated under reduced pressure and crystallized from n-hexane-diethyl ether. The crystals were collected by filtration and air-dried to obtain the title compound (60 mg).

NMR spectrum (DMSO-d<sub>6</sub>, 100°C) δppm: 8.13(2H,dd,J=2,5Hz), 7.40-7.25(5H,m), 6.76(2H,dd,J=2,5Hz), 5.13(2H,s), 5.07(1H,dd,J=4,9Hz), 4.38-4.28(1H,m), 4.23(1H,d,J=18Hz), 3.84-3.73(2H,m), 3.52-3.23(4H,m), 3.17(1H,d,J=11Hz), 3.04-2.92(1H,m), 1.90-1.60(4H,m)

<Step 7>

Synthesis of 1,4-diaza-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0450]** The procedure of Reference Example 1 <Step 8> was repeated by using the compound obtained in Step 6. To a solution of this compound (100 mg) in methanol (2.4 ml) was added 10% palladium-carbon (20 mg). After stirring at room temperature for 1 hour under a hydrogen atmosphere, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography [ChromatorexNH™] (eluent; ethyl acetate : methanol = 9:1) to obtain the title compound (60 mg).

NMR spectrum (\*CDCl<sub>3</sub>) δppm: 8.31-8.22(2H,m), 6.72-6.63(2H,m), 5.00(1H,dd,J=4,8Hz), 3.96-3.88(1H,m), 3.65-3.28(7H,m), 3.19-3.10(1H,m), 2.66(1H,dd,J=8,13Hz), 2.00-1.55(4H,m)

(Reference Example 4)

<Step 1>

Synthesis of 1,4-diaza-1'-benzyl-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0451]** The procedure of Reference Example 2 <Step 1> was repeated by using the compound obtained in Reference Example 3 <Step 4> (50 mg) to obtain the title compound (15 mg).

NMR spectrum (<sup>1</sup>H, CDCl<sub>3</sub>) δppm: 7.40-7.25(5H,m), 4.94(1H,dd,J=4,8Hz), 3.83(1H,d,J=11Hz), 3.62-3.37(5H,m), 3.14(1H,d,J=11Hz), 2.62(1H,dd,J=8,13Hz), 2.65-2.35(4H,m), 1.95-1.53(4H,m)

<Step 2>

Synthesis of 1,4-diaza-1'-benzyl-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

**[0452]** The procedure of Reference Example 2 <Step 2> was repeated by using the compound obtained in Step 1 (10.0 mg) to obtain the title compound quantitatively.

<Step 3>

**[0453]** The procedure of Example 1 <Step A-1> was repeated by using the compound obtained in Step 1 (10 mg) to obtain the title compound (22 mg).

(Reference Example 5)

Synthesis of 1,4-diaza-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one

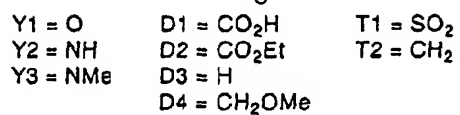
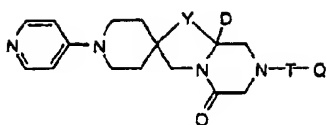
**[0454]** The procedure of Reference Example 1 <Step 8> was repeated by using the compound obtained in Reference Example 3 <Step 5> (10.0 mg) to obtain the title compound (6.0 mg).

NMR spectrum (<sup>1</sup>H, CDCl<sub>3</sub>) δppm: 4.97(1H,dd,J=4,8Hz), 3.87(1H,d,J=12Hz), 3.59(1H,d,J=18Hz), 3.51-3.38(2H,m), 3.15(1H,d,J=12Hz), 3.15-2.97(2H,m), 2.94-2.77(2H,m), 2.63(1H,dd,J=8,13Hz), 1.88-1.63(4H,m)

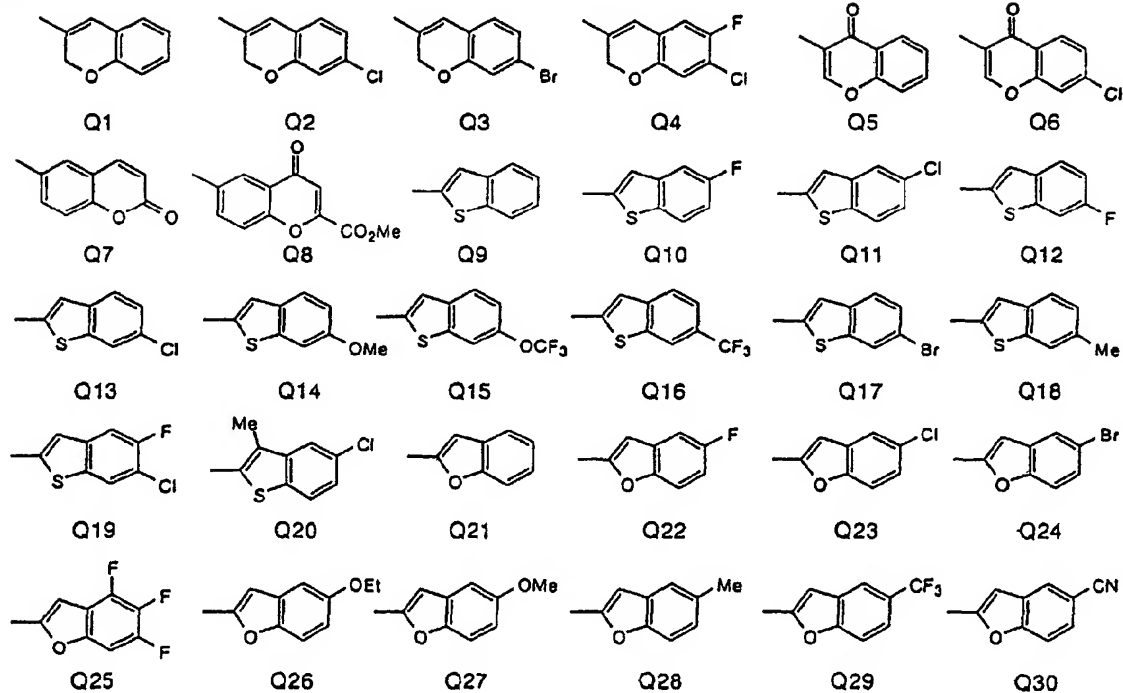
**[0455]** The structures of the compounds of the present invention obtained in Examples mentioned above are shown in FIGs. 1 - 9. The synthesis routes of the compounds of the present invention are shown in FIGs. 11 - 20.

**[0456]** Further, the NMR spectrum data of these Examples are shown in FIGs. 21 - 32.

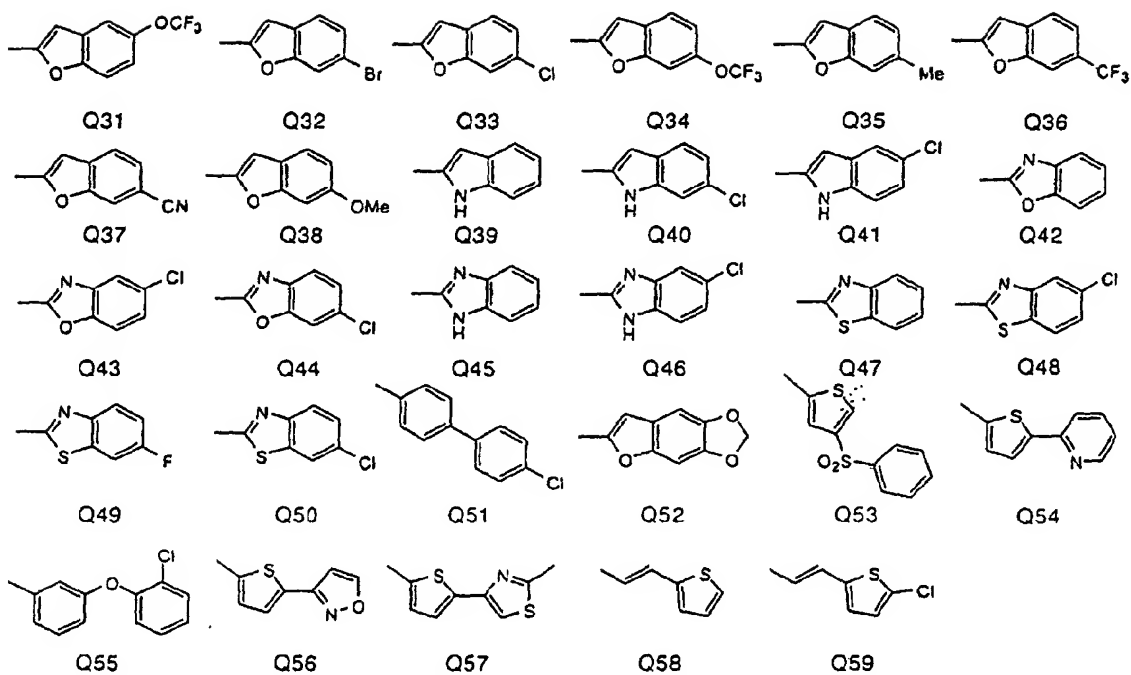
**[0457]** In addition, the compounds mentioned below are also synthesized in the same manner as in Examples.



Q:







Ex. No.	Y	D	T	Q
83	Y1	D1	T1	Q1
84	Y1	D1	T1	Q2
85	Y1	D1	T1	Q3
86	Y1	D1	T1	Q4
87	Y1	D1	T1	Q5
88	Y1	D1	T1	Q6
89	Y1	D1	T1	Q7
90	Y1	D1	T1	Q8
91	Y1	D1	T1	Q9
92	Y1	D1	T1	Q10
93	Y1	D1	T1	Q11
94	Y1	D1	T1	Q12
95	Y1	D1	T1	Q13
96	Y1	D1	T1	Q14
97	Y1	D1	T1	Q15
98	Y1	D1	T1	Q16
99	Y1	D1	T1	Q17
100	Y1	D1	T1	Q18
101	Y1	D1	T1	Q19
102	Y1	D1	T1	Q20
103	Y1	D1	T1	Q21
104	Y1	D1	T1	Q22
105	Y1	D1	T1	Q23
106	Y1	D1	T1	Q24
107	Y1	D1	T1	Q25

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	108	Y1	D1	T1	Q26
	109	Y1	D1	T1	Q27
	110	Y1	D1	T1	Q28
	111	Y1	D1	T1	Q29
	112	Y1	D1	T1	Q30
10	113	Y1	D1	T1	Q31
	114	Y1	D1	T1	Q32
	115	Y1	D1	T1	Q33
	116	Y1	D1	T1	Q34
	117	Y1	D1	T1	Q35
15	118	Y1	D1	T1	Q36
	119	Y1	D1	T1	Q37
	120	Y1	D1	T1	Q38
	121	Y1	D1	T1	Q39
	122	Y1	D1	T1	Q40
20	123	Y1	D1	T1	Q41
	124	Y1	D1	T1	Q42
	125	Y1	D1	T1	Q43
	126	Y1	D1	T1	Q44
	127	Y1	D1	T1	Q45
25	128	Y1	D1	T1	Q46
	129	Y1	D1	T1	Q47
	130	Y1	D1	T1	Q48
	131	Y1	D1	T1	Q49
	132	Y1	D1	T1	Q50
30	133	Y1	D1	T1	Q51
	134	Y1	D1	T1	Q52
	135	Y1	D1	T1	Q53
	136	Y1	D1	T1	Q54
	137	Y1	D1	T1	Q55
35	138	Y1	D1	T1	Q56
	139	Y1	D1	T1	Q57
	140	Y1	D1	T1	Q58
	141	Y1	D1	T1	Q59
	142	Y1	D2	T1	Q1
40	143	Y1	D2	T1	Q2
	144	Y1	D2	T1	Q3
	145	Y1	D2	T1	Q4
	146	Y1	D2	T1	Q5
	147	Y1	D2	T1	Q6
45	148	Y1	D2	T1	Q7
	149	Y1	D2	T1	Q8
	150	Y1	D2	T1	Q9
	151	Y1	D2	T1	Q10
	152	Y1	D2	T1	Q11
50	153	Y1	D2	T1	Q12
	154	Y1	D2	T1	Q13
	155	Y1	D2	T1	Q14
	156	Y1	D2	T1	Q15

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	157	Y1	D2	T1	Q16
	158	Y1	D2	T1	Q17
	159	Y1	D2	T1	Q18
	160	Y1	D2	T1	Q19
	161	Y1	D2	T1	Q20
10	162	Y1	D2	T1	Q21
	163	Y1	D2	T1	Q22
	164	Y1	D2	T1	Q23
	165	Y1	D2	T1	Q24
	166	Y1	D2	T1	Q25
15	167	Y1	D2	T1	Q26
	168	Y1	D2	T1	Q27
	169	Y1	D2	T1	Q28
	170	Y1	D2	T1	Q29
20	171	Y1	D2	T1	Q30
	172	Y1	D2	T1	Q31
	173	Y1	D2	T1	Q32
	174	Y1	D2	T1	Q33
	175	Y1	D2	T1	Q34
25	176	Y1	D2	T1	Q35
	177	Y1	D2	T1	Q36
	178	Y1	D2	T1	Q37
	179	Y1	D2	T1	Q38
30	180	Y1	D2	T1	Q39
	181	Y1	D2	T1	Q40
	182	Y1	D2	T1	Q41
	183	Y1	D2	T1	Q42
	184	Y1	D2	T1	Q43
35	185	Y1	D2	T1	Q44
	186	Y1	D2	T1	Q45
	187	Y1	D2	T1	Q46
	188	Y1	D2	T1	Q47
40	189	Y1	D2	T1	Q48
	190	Y1	D2	T1	Q49
	191	Y1	D2	T1	Q50
	192	Y1	D2	T1	Q51
	193	Y1	D2	T1	Q52
45	194	Y1	D2	T1	Q53
	195	Y1	D2	T1	Q54
	196	Y1	D2	T1	Q55
	197	Y1	D2	T1	Q56
50	198	Y1	D2	T1	Q57
	199	Y1	D2	T1	Q58
	200	Y1	D2	T1	Q59
	201	Y1	D3	T1	Q1
	202	Y1	D3	T1	Q2
55	203	Y1	D3	T1	Q3
	204	Y1	D3	T1	Q4
	205	Y1	D3	T1	Q5

**EP 1 191 028 A1**

(continued)

	Ex. No.	Y	D	T	Q
5	206	Y1	D3	T1	Q6
	207	Y1	D3	T1	Q7
	208	Y1	D3	T1	Q8
	209	Y1	D3	T1	Q9
	210	Y1	D3	T1	Q10
10	211	Y1	D3	T1	Q11
	212	Y1	D3	T1	Q12
	213	Y1	D3	T1	Q13
	214	Y1	D3	T1	Q14
	215	Y1	D3	T1	Q15
15	216	Y1	D3	T1	Q16
	217	Y1	D3	T1	Q17
	218	Y1	D3	T1	Q18
	219	Y1	D3	T1	Q19
20	220	Y1	D3	T1	Q20
	221	Y1	D3	T1	Q21
	222	Y1	D3	T1	Q22
	223	Y1	D3	T1	Q23
	224	Y1	D3	T1	Q24
25	225	Y1	D3	T1	Q25
	226	Y1	D3	T1	Q26
	227	Y1	D3	T1	Q27
	228	Y1	D3	T1	Q28
30	229	Y1	D3	T1	Q29
	230	Y1	D3	T1	Q30
	231	Y1	D3	T1	Q31
	232	Y1	D3	T2	Q1
	233	Y1	D3	T2	Q2
35	234	Y1	D3	T2	Q3
	235	Y1	D3	T2	Q4
	236	Y1	D3	T2	Q5
	237	Y1	D3	T2	Q6
40	238	Y1	D3	T2	Q7
	239	Y1	D3	T2	Q8
	240	Y1	D3	T2	Q9
	241	Y1	D3	T2	Q10
	242	Y1	D3	T2	Q11
45	243	Y1	D3	T2	Q12
	244	Y1	D3	T2	Q13
	245	Y1	D3	T2	Q14
	246	Y1	D3	T2	Q15
50	247	Y1	D3	T2	Q16
	248	Y1	D3	T2	Q17
	249	Y1	D3	T2	Q18
	250	Y1	D3	T2	Q19
	251	Y1	D3	T2	Q20
55	252	Y1	D3	T2	Q21
	253	Y1	D3	T2	Q22
	254	Y1	D3	T2	Q23

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	255	Y1	D3	T2	Q24
	256	Y1	D3	T2	Q25
	257	Y1	D3	T2	Q26
	258	Y1	D3	T2	Q27
	259	Y1	D3	T2	Q28
10	260	Y1	D3	T2	Q29
	261	Y1	D3	T2	Q30
	262	Y1	D3	T2	Q3]
	263	Y2	D3	T1	Q1
	264	Y2	D3	T1	Q2
15	265	Y2	D3	T1	Q3
	266	Y2	D3	T1	Q4
	267	Y2	D3	T1	Q5
	268	Y2	D3	T1	Q6
	269	Y2	D3	T1	Q7
20	270	Y2	D3	T1	Q8
	271	Y2	D3	T1	Q9
	272	Y2	D3	T1	Q10
	273	Y2	D3	T1	Q11
	274	Y2	D3	T1	Q12
25	275	Y2	D3	T1	Q13
	276	Y2	D3	T1	Q14
	277	Y2	D3	T1	Q15
	278	Y2	D3	T1	Q16
	279	Y2	D3	T1	Q17
30	280	Y2	D3	T1	Q18
	281	Y2	D3	T1	Q19
	282	Y2	D3	T1	Q20
	283	Y2	D3	T1	Q21
	284	Y2	D3	T1	Q22
35	285	Y2	D3	T1	Q23
	286	Y2	D3	T1	Q24
	287	Y2	D3	T1	Q25
	288	Y2	D3	T1	Q26
	289	Y2	D3	T1	Q27
40	290	Y2	D3	T1	Q28
	291	Y2	D3	T1	Q29
	292	Y2	D3	T1	Q30
	293	Y2	D3	T1	Q31
	294	Y2	D3	T2	Q1
45	295	Y2	D3	T2	Q2
	296	Y2	D3	T2	Q3
	297	Y2	D3	T2	Q4
	298	Y2	D3	T2	Q5
	299	Y2	D3	T2	Q6
50	300	Y2	D3	T2	Q7
	301	Y2	D3	T2	Q8
	302	Y2	D3	T2	Q9
	303	Y2	D3	T2	Q10

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	304	Y2	D3	T2	Q11
	305	Y2	D3	T2	Q12
	306	Y2	D3	T2	Q13
	307	Y2	D3	T2	Q14
	308	Y2	D3	T2	Q15
10	309	Y2	D3	T2	Q16
	310	Y2	D3	T2	Q17
	311	Y2	D3	T2	Q18
	312	Y2	D3	T2	Q19
	313	Y2	D3	T2	Q20
15	314	Y2	D3	T2	Q21
	315	Y2	D3	T2	Q22
	316	Y2	D3	T2	Q23
	317	Y2	D3	T2	Q24
	318	Y2	D3	T2	Q25
20	319	Y2	D3	T2	Q26
	320	Y2	D3	T2	Q27
	321	Y2	D3	T2	Q28
	322	Y2	D3	T2	Q29
	323	Y2	D3	T2	Q30
25	324	Y2	D3	T2	Q31
	325	Y3	D3	T1	Q1
	326	Y3	D3	T1	Q2
	327	Y3	D3	T1	Q3
	328	Y3	D3	T1	Q4
30	329	Y3	D3	T1	Q5
	330	Y3	D3	T1	Q6
	331	Y3	D3	T1	Q7
	332	Y3	D3	T1	Q8
	333	Y3	D3	T1	Q9
35	334	Y3	D3	T1	Q10
	335	Y3	D3	T1	Q11
	336	Y3	D3	T1	Q12
	337	Y3	D3	T1	Q13
	338	Y3	D3	T1	Q14
40	339	Y3	D3	T1	Q15
	340	Y3	D3	T1	Q16
	341	Y3	D3	T1	Q17
	342	Y3	D3	T1	Q18
	343	Y3	D3	T1	Q19
45	344	Y3	D3	T1	Q20
	345	Y3	D3	T1	Q21
	346	Y3	D3	T1	Q22
	347	Y3	D3	T1	Q23
	348	Y3	D3	T1	Q24
50	349	Y3	D3	T1	Q25
	350	Y3	D3	T1	Q26
	351	Y3	D3	T1	Q27
	352	Y3	D3	T1	Q28

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	353	Y3	D3	T1	Q29
	354	Y3	D3	T1	Q30
	355	Y3	D3	T1	Q31
	356	Y3	D3	T2	Q1
	357	Y3	D3	T2	Q2
10	358	Y3	D3	T2	Q3
	359	Y3	D3	T2	Q4
	360	Y3	D3	T2	Q5
	361	Y3	D3	T2	Q6
	362	Y3	D3	T2	Q7
15	363	Y3	D3	T2	Q8
	364	Y3	D3	T2	Q9
	365	Y3	D3	T2	Q10
	366	Y3	D3	T2	Q11
	367	Y3	D3	T2	Q12
20	368	Y3	D3	T2	Q13
	369	Y3	D3	T2	Q14
	370	Y3	D3	T2	Q15
	371	Y3	D3	T2	Q16
	372	Y3	D3	T2	Q17
25	373	Y3	D3	T2	Q18
	374	Y3	D3	T2	Q19
	375	Y3	D3	T2	Q20
	376	Y3	D3	T2	Q21
	377	Y3	D3	T2	Q22
30	378	Y3	D3	T2	Q23
	379	Y3	D3	T2	Q24
	380	Y3	D3	T2	Q25
	381	Y3	D3	T2	Q26
	382	Y3	D3	T2	Q27
35	383	Y3	D3	T2	Q28
	384	Y3	D3	T2	Q29
	385	Y3	D3	T2	Q30
	386	Y3	D3	T2	Q31
	387	Y1	D4	T1	Q1
40	388	Y1	D4	T1	Q2
	389	Y1	D4	T1	Q3
	390	Y1	D4	T1	Q4
	391	Y1	D4	T1	Q5
	392	Y1	D4	T1	Q6
45	393	Y1	D4	T1	Q7
	394	Y1	D4	T1	Q8
	395	Y1	D4	T1	Q9
	396	Y1	D4	T1	Q10
	397	Y1	D4	T1	Q11
50	398	Y1	D4	T1	Q12
	399	Y1	D4	T1	Q13
	400	Y1	D4	T1	Q14
	401	Y1	D4	T1	Q15

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	402	Y1	D4	T1	Q16
	403	Y1	D4	T1	Q17
	404	Y1	D4	T1	Q18
	405	Y1	D4	T1	Q19
	406	Y1	D4	T1	Q20
10	407	Y1	D4	T1	Q21
	408	Y1	D4	T1	Q22
	409	Y1	D4	T1	Q23
	410	Y1	D4	T1	Q24
	411	Y1	D4	T1	Q25
15	412	Y1	D4	T1	Q26
	413	Y1	D4	T1	Q27
	414	Y1	D4	T1	Q28
	415	Y1	D4	T1	Q29
	416	Y1	D4	T1	Q30
20	417	Y1	D4	T1	Q31
	418	Y1	D4	T2	Q1
	419	Y1	D4	T2	Q2
	420	Y1	D4	T2	Q3
	421	Y1	D4	T2	Q4
25	422	Y1	D4	T2	Q5
	423	Y1	D4	T2	Q6
	424	Y1	D4	T2	Q7
	425	Y1	D4	T2	Q8
	426	Y1	D4	T2	Q9
30	427	Y1	D4	T2	Q10
	428	Y1	D4	T2	Q11
	429	Y1	D4	T2	Q12
	430	Y1	D4	T2	Q13
	431	Y1	D4	T2	Q14
35	432	Y1	D4	T2	Q15
	433	Y1	D4	T2	Q16
	434	Y1	D4	T2	Q17
	435	Y1	D4	T2	Q18
	436	Y1	D4	T2	Q19
40	437	Y1	D4	T2	Q20
	438	Y1	D4	T2	Q21
	439	Y1	D4	T2	Q22
	440	Y1	D4	T2	Q23
	441	Y1	D4	T2	Q24
45	442	Y1	D4	T2	Q25
	443	Y1	D4	T2	Q26
	444	Y1	D4	T2	Q27
	445	Y1	D4	T2	Q28
	446	Y1	D4	T2	Q29
50	447	Y1	D4	T2	Q30
	448	Y1	D4	T2	Q31
	449	Y2	D4	T1	Q1
	450	Y2	D4	T1	Q2



EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	451	Y2	D4	T1	Q3
	452	Y2	D4	T1	Q4
	453	Y2	D4	T1	Q5
	454	Y2	D4	T1	Q6
	455	Y2	D4	T1	Q7
10	456	Y2	D4	T1	Q8
	457	Y2	D4	T1	Q9
	458	Y2	D4	T1	Q10
	459	Y2	D4	T1	Q11
	460	Y2	D4	T1	Q12
15	461	Y2	D4	T1	Q13
	462	Y2	D4	T1	Q14
	463	Y2	D4	T1	Q15
	464	Y2	D4	T1	Q16
	465	Y2	D4	T1	Q17
20	466	Y2	D4	T1	Q18
	467	Y2	D4	T1	Q19
	468	Y2	D4	T1	Q20
	469	Y2	D4	T1	Q21
	470	Y2	D4	T1	Q22
25	471	Y2	D4	T1	Q23
	472	Y2	D4	T1	Q24
	473	Y2	D4	T1	Q25
	474	Y2	D4	T1	Q26
	475	Y2	D4	T1	Q27
30	476	Y2	D4	T1	Q28
	477	Y2	D4	T1	Q29
	478	Y2	D4	T1	Q30
	479	Y2	D4	T1	Q31
	480	Y2	D4	T2	Q1
35	481	Y2	D4	T2	Q2
	482	Y2	D4	T2	Q3
	483	Y2	D4	T2	Q4
	484	Y2	D4	T2	Q5
	485	Y2	D4	T2	Q6
40	486	Y2	D4	T2	Q7
	487	Y2	D4	T2	Q8
	488	Y2	D4	T2	Q9
	489	Y2	D4	T2	Q10
	490	Y2	D4	T2	Q11
45	491	Y2	D4	T2	Q12
	492	Y2	D4	T2	Q13
	493	Y2	D4	T2	Q14
	494	Y2	D4	T2	Q15
	495	Y2	D4	T2	Q16
50	496	Y2	D4	T2	Q17
	497	Y2	D4	T2	Q18
	498	Y2	D4	T2	Q19
	499	Y2	D4	T2	Q20

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	500	Y2	D4	T2	Q21
	501	Y2	D4	T2	Q22
	502	Y2	D4	T2	Q23
	503	Y2	D4	T2	Q24
	504	Y2	D4	T2	Q25
10	505	Y2	D4	T2	Q26
	506	Y2	D4	T2	Q27
	507	Y2	D4	T2	Q28
	508	Y2	D4	T2	Q29
	509	Y2	D4	T2	Q30
15	510	Y2	D4	T2	Q31
	511	Y3	D4	T1	Q1
	512	Y3	D4	T1	Q2
	513	Y3	D4	T1	Q3
	514	Y3	D4	T1	Q4
20	515	Y3	D4	T1	Q5
	516	Y3	D4	T1	Q6
	517	Y3	D4	T1	Q7
	518	Y3	D4	T1	Q8
	519	Y3	D4	T1	Q9
25	520	Y3	D4	T1	Q10
	521	Y3	D4	T1	Q11
	522	Y3	D4	T1	Q12
	523	Y3	D4	T1	Q13
	524	Y3	D4	T1	Q14
30	525	Y3	D4	T1	Q15
	526	Y3	D4	T1	Q16
	527	Y3	D4	T1	Q17
	528	Y3	D4	T1	Q18
	529	Y3	D4	T1	Q19
35	530	Y3	D4	T1	Q20
	531	Y3	D4	T1	Q21
	532	Y3	D4	T1	Q22
	533	Y3	D4	T1	Q23
	534	Y3	D4	T1	Q24
40	535	Y3	D4	T1	Q25
	536	Y3	D4	T1	Q26
	537	Y3	D4	T1	Q27
	538	Y3	D4	T1	Q28
	539	Y3	D4	T1	Q29
45	540	Y3	D4	T1	Q30
	541	Y3	D4	T1	Q31
	542	Y3	D4	T2	Q1
	543	Y3	D4	T2	Q2
	544	Y3	D4	T2	Q3
50	545	Y3	D4	T2	Q4
	546	Y3	D4	T2	Q5
	547	Y3	D4	T2	Q6
	548	Y3	D4	T2	Q7

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	549	Y3	D4	T2	Q8
	550	Y3	D4	T2	Q9
	551	Y3	D4	T2	Q10
	552	Y3	D4	T2	Q11
	553	Y3	D4	T2	Q12
10	554	Y3	D4	T2	Q13
	555	Y3	D4	T2	Q14
	556	Y3	D4	T2	Q15
	557	Y3	D4	T2	Q16
	558	Y3	D4	T2	Q17
15	559	Y3	D4	T2	Q18
	560	Y3	D4	T2	Q19
	561	Y3	D4	T2	Q20
	562	Y3	D4	T2	Q21
	563	Y3	D4	T2	Q22
20	564	Y3	D4	T2	Q23
	565	Y3	D4	T2	Q24
	566	Y3	D4	T2	Q25
	567	Y3	D4	T2	Q26
	568	Y3	D4	T2	Q27
25	569	Y3	D4	T2	Q28
	570	Y3	D4	T2	Q29
	571	Y3	D4	T2	Q30
	572	Y3	D4	T2	Q31
	573	Y1	D3	T1	Q32
30	574	Y1	D3	T1	Q33
	575	Y1	D3	T1	Q34
	576	Y1	D3	T1	Q35
	577-	Y1	D3	T1	Q36
	578	Y1	D3	T1	Q37
35	579	Y1	D3	T1	Q38
	580	Y1	D3	T1	Q39
	581	Y1	D3	T1	Q40
	582	Y1	D3	T1	Q41
	583	Y1	D3	T1	Q42
40	584	Y1	D3	T1	Q43
	585	Y1	D3	T1	Q44
	586	Y1	D3	T1	Q45
	587	Y1	D3	T1	Q46
	588	Y1	D3	T1	Q47
45	589	Y1	D3	T1	Q48
	590	Y1	D3	T1	Q49
	591	Y1	D3	T1	Q50
	592	Y1	D3	T1	Q51
	593	Y1	D3	T1	Q52
50	594	Y1	D3	T1	Q53
	595	Y1	D3	T1	Q54
	596	Y1	D3	T1	Q55
	597	Y1	D3	T1	Q56

**EP 1 191 028 A1**

(continued)

	Ex. No.	Y	D	T	Q
5	598	Y1	D3	T1	Q57
	599	Y1	D3	T1	Q58
	600	Y1	D3	T1	Q59
	601	Y2	D3	T1	Q32
	602	Y2	D3	T1	Q33
10	603	Y2	D3	T1	Q34
	604	Y2	D3	T1	Q35
	605	Y2	D3	T1	Q36
	606	Y2	D3	T1	Q37
	607	Y2	D3	T1	Q38
15	608	Y2	D3	T1	Q39
	609	Y2	D3	T1	Q40
	610	Y2	D3	T1	Q41
	611	Y2	D3	T1	Q42
	612	Y2	D3	T1	Q43
20	613	Y2	D3	T1	Q44
	614	Y2	D3	T1	Q45
	615	Y2	D3	T1	Q46
	616	Y2	D3	T1	Q47
	617	Y2	D3	T1	Q48
25	618	Y2	D3	T1	Q49
	619	Y2	D3	T1	Q50
	620	Y2	D3	T1	Q51
	621	Y2	D3	T1	Q52
	622	Y2	D3	T1	Q53
30	623	Y2	D3	T1	Q54
	624	Y2	D3	T1	Q55
	625	Y2	D3	T1	Q56
	626	Y2	D3	T1	Q57
	627	Y2	D3	T1	Q58
35	628	Y2	D3	T1	Q59
	629	Y3	D3	T1	Q32
	630	Y3	D3	T1	Q33
	631	Y3	D3	T1	Q34
	632	Y3	D3	T1	Q35
40	633	Y3	D3	T1	Q36
	634	Y3	D3	T1	Q37
	635	Y3	D3	T1	Q38
	636	Y3	D3	T1	Q39
	637	Y3	D3	T1	Q40
45	638	Y3	D3	T1	Q41
	639	Y3	D3	T1	Q42
	640	Y3	D3	T1	Q43
	641	Y3	D3	T1	Q44
	642	Y3	D3	T1	Q45
50	643	Y3	D3	T1	Q46
	644	Y3	D3	T1	Q47
	645	Y3	D3	T1	Q48
	646	Y3	D3	T1	Q49

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	647	Y3	D3	T1	Q50
	648	Y3	D3	T1	Q51
	649	Y3	D3	T1	Q52
	650	Y3	D3	T1	Q53
	651	Y3	D3	T1	Q54
10	652	Y3	D3	T1	Q55
	653	Y3	D3	T1	Q56
	654	Y3	D3	T1	Q57
	655	Y3	D3	T1	Q58
	656	Y3	D3	T1	Q59
15	657	Y1	D4	T1	Q32
	658	Y1	D4	T1	Q33
	659	Y1	D4	T1	Q34
	660	Y1	D4	T1	Q35
	661	Y1	D4	T1	Q36
20	662	Y1	D4	T1	Q37
	663	Y1	D4	T1	Q38
	664	Y1	D4	T1	Q39
	665	Y1	D4	T1	Q40
	666	Y1	D4	T1	Q41
25	667	Y1	D4	T1	Q42
	668	Y1	D4	T1	Q43
	669	Y1	D4	T1	Q44
	670	Y1	D4	T1	Q45
	671	Y1	D4	T1	Q46
30	672	Y1	D4	T1	Q47
	673	Y1	D4	T1	Q48
	674	Y1	D4	T1	Q49
	675	Y1	D4	T1	Q50
	676	Y1	D4	T1	Q51
35	677	Y1	D4	T1	Q52
	678	Y1	D4	T1	Q53
	679	Y1	D4	T1	Q54
	680	Y1	D4	T1	Q55
	681	Y1	D4	T1	Q56
40	682	Y1	D4	T1	Q57
	683	Y1	D4	T1	Q58
	684	Y1	D4	T1	Q59
	685	Y2	D4	T1	Q32
	686	Y2	D4	T1	Q33
45	687	Y2	D4	T1	Q34
	688	Y2	D4	T1	Q35
	689	Y2	D4	T1	Q36
	690	Y2	D4	T1	Q37
	691	Y2	D4	T1	Q38
50	692	Y2	D4	T1	Q39
	693	Y2	D4	T1	Q40
	694	Y2	D4	T1	Q41
	695	Y2	D4	T1	Q42

EP 1 191 028 A1

(continued)

	Ex. No.	Y	D	T	Q
5	696	Y2	D4	T1	Q43
	697	Y2	D4	T1	Q44
	698	Y2	D4	T1	Q45
	699	Y2	D4	T1	Q46
	700	Y2	D4	T1	Q47
10	701	Y2	D4	T1	Q48
	702	Y2	D4	T1	Q49
	703	Y2	D4	T1	Q50
	704	Y2	D4	T1	Q51
	705	Y2	D4	T1	Q52
15	706	Y2	D4	T1	Q53
	707	Y2	D4	T1	Q54
	708	Y2	D4	T1	Q55
	709	Y2	D4	T1	Q56
20	710	Y2	D4	T1	Q57
	711	Y2	D4	T1	Q58
	712	Y2	D4	T1	Q59
	713	Y3	D4	T1	Q32
	714	Y3	D4	T1	Q33
25	715	Y3	D4	T1	Q34
	716	Y3	D4	T1	Q35
	717	Y3	D4	T1	Q36
	718	Y3	D4	T1	Q37
30	719	Y3	D4	T1	Q38
	720	Y3	D4	T1	Q39
	721	Y3	D4	T1	Q40
	722	Y3	D4	T1	Q41
	723	Y3	D4	T1	Q42
35	724	Y3	D4	T1	Q43
	725	Y3	D4	T1	Q44
	726	Y3	D4	T1	Q45
	727	Y3	D4	T1	Q46
40	728	Y3	D4	T1	Q47
	729	Y3	D4	T1	Q48
	730	Y3	D4	T1	Q49
	731	Y3	D4	T1	Q50
	732	Y3	D4	T1	Q51
45	733	Y3	D4	T1	Q52
	734	Y3	D4	T1	Q53
	735	Y3	D4	T1	Q54
	736	Y3	D4	T1	Q55
50	737	Y3	D4	T1	Q56
	738	Y3	D4	T1	Q57
	739	Y3	D4	T1	Q58
	740	Y3	D4	T1	Q59

55

## &lt;Examples of X ray crystallography&gt;

A. X ray crystallography of FXa and (-) optical isomer of Example 1 of the present invention (hereinafter referred to as Compound A)

(A-1) Purification and crystallization of human FXa from which Gla domain has been removed (hereinafter referred to as Des-Gla-FXa)

**[0458]** A purified sample of human FXa was purchased from Enzyme Research Laboratories, Inc. and the sample was digested with a protease in accordance with J. Biol. Chem., 271, 16614-16620(1996) to remove Gla domain (1-44 (chymotrypsin No.)). The Des-Gla-FXa was purified by using Mono-P (Amersham Pharmacia Biotech Inc.), and the crystallization was accomplished by hanging drop vapor diffusion method.

**[0459]** Good crystals were obtained when vapor diffusion of drops produced by mixing an equivalent amount of the concentrated sample and 26% (w/v) PEG1500 were conducted against 26%(w/v) PEG1500 solution.

**[0460]** The complex crystal was subjected to X-ray diffraction experiment at a low temperature of -180°C using diffractometer R-AXIS (Rigaku K.K.) and data set was collected at 2.8 Å resolution. The complex crystal was orthorhombic, and the space group was  $P2_12_12_1$ , and the lattice constant was  $a = 72.7$ ,  $b = 78.17$ , and  $c = 56.04$  Å. This crystal contained 1 molecule in the asymmetric unit, and the  $V_m$  value was 2.2 Å<sup>3</sup>/Dalton.

**[0461]** The structure was analyzed by molecule replacement method using REPLACE (Tong, 1993) included in crystallographic packaging program Xsight (MSI Inc.). Ihcg of protein data bank was used for the initial structure model.

(A-2) Construction of crystal structure and refinement

**[0462]** By using the three dimensional electron density map obtained by the procedure as described above, detailed fitting of A chain (Ile16 to Thr244) and B chain (Lys877 to Leu137) (in chymotrypsin No.) of the FXa was conducted.

**[0463]** These operations were accomplished by manually operating the model building program Xfit included in the packaging program XtalView (McRee, 1993).

**[0464]** Crystallographic structure of these atom coordinates was refined by using X-PLOR (Brunger, 1987). The refinement was conducted by repeating the calculation by X-PLOR and adjustment of the atom position by manual adjustment to thereby minimize R factor, and this refinement was continued until the value of approximately 20% was obtained.

**[0465]** Coordinate data (PDB format) of the crystal structure of the FXa - Compound A complex after the refinement are shown in Table A.

**[0466]** The columns are as described below. Column 1: record ID of the PDB file; column 2: serial number of coordinate in the PDB file; column 3: atom name; column 4: name of the amino acid residue; column 5: amino acid residue No. (chymotrypsin No.); column 6: X coordinate of the atom; column 7: Y coordinate of the atom; column 8: Z coordinate of the atom; column 9: filling factor (fixed to 1.0); and column 10: temperature factor.

**[0467]** The name of the amino acid residue of Compound A is indicated as M32 for convenience. Hydrogen atoms in the coordinate data are those generated in the course of calculation on program X-PLOR, and the data do not indicate accurate position of the hydrogen atoms.

**[0468]** On the bases of such data, FIG. 37 shows the structure of the FXa (ribbon diagram), and FIG. 38 shows the crystal structure of the FXa - Compound A complex (ribbon diagram).

**[0469]** FIGS. 37 and 38 were prepared by using the program MOLSCRIPT (Kraulis, P., J. Appl. Crystallogr., 24, 946-950(1991)).

**[0470]** FIG. 39 shows active sites of the human FXa.

**[0471]** FIG. 40 shows active sites of the human FXa - Compound A complex.

**[0472]** The regions corresponding to the S1 pocket and the S3 pocket are surrounded with a broken line for ease of understanding pharmacophore of the present invention.

**[0473]** FIG. 41 shows the stereo view of the active sites of the human FXa - Compound A complex. FIG. 41 was prepared by using the program MOLSCRIPT.

**[0474]** As a result of X-ray crystallographic analysis, it was found out that the naphthalene ring moiety of the Compound A is bonded to S1 pocket of the FXa by hydrophobic interaction; the chlorine atom added to the naphthalene has undergone interaction with the benzene ring moiety of the Tyr228 side chain in the S1 pocket; the Compound A has not undergone electrostatic interaction with the Asp189 of the FXa in the S1 pocket; and the binding mode of the Compound A to the S1 pocket is totally different from the binding mode of DX-9065a and FX-2212a which are known FXa inhibitors whose structure of the complex has been found out.

**[0475]** With regard to the remarkably high selectivity of the Compound A for trypsin, it is believed that steric hindrance is induced between the Compound A and Ser 190 of the trypsin and such steric hindrance is a factor for the high

selectivity for the trypsin.

**[0476]** 4-aminopyridine moiety of the Compound A binds to the S3 pocket by the interaction between the basic moiety of the 4-aminopyridine moiety and the electrically negative condition of the S3 pocket, and such situation is believed to contribute for the selectivity of the Compound A for trypsin, thrombin, protein C and tissue plasminogen activator.

**[0477]** Furthermore, hydrogen bond is formed between the carbonyl oxygen atom of the Compound A and the NH group of the Gly218 backbone. Although the present invention is preferably not confined by any hypothesis, the structural activity correlation of the compound of the present invention is believed to indicate that this bond is not necessary for the inhibition of the FXa, but has secondary effects such as increase of the FXa inhibitory activity.

Construction of the model structure of the compound - FXa complex

**[0478]** Insight II, Discover, and Search Compare as mentioned below are names of computer programs which are commercially available from Molecular Simulations Inc., San Diego, CA, USA.

Two Reference compounds

**[0479]**

Compound B: 4-[3-(6-chloronaphthalen-2-ylsulfoneamide)-2-[1-(4-pyridyl)piperidin-4-ylmethyl]aminopropionyl]-1,1-dioxothiomorpholine (The compound of Japanese Patent Application No. 11-180909, Example 8); and Compound C: (R)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one (The compound of WO99/33805, Example 60) (Note that the production process of these compounds are found in the specifications of these patent applications. The structural formulae are shown in FIG. 10.) Three-dimensional model structure of these Compounds B and C were prepared on Insight II, and the model structure was optimized by molecular mechanics calculation by using Discover. Subsequently, by manual operation on Insight II, the halogenonaphthalene moiety of the Compound B and that of the Compound C were overlaid with the halogenonaphthalene moiety of the Compound A in the crystal structure of the complex obtained in the crystal structure analysis in the Examples of the present invention to thereby construct the model initial structure of the complex of the FXa and the Compound B or C.

Conformational search of the compound

**[0480]** Conformation of the Compounds B and C other than the halogenonaphthalene moiety was searched by using Search Compare with the halogenonaphthalene moiety of the Compounds B and C fixed in the S1 pocket.

**[0481]** The conformation was generated by systematically rotating the bonds in the Compound B or C which were estimated to be rotatable. The rotation angle of the bond was 60 degrees to 300 degrees at an increment of 120 degrees in dihedral angle in the case of the bond between Sp3 atoms; and 0 degree to 330 degrees at an increment of 30 degrees in dihedral angle in the case of the bond between Sp3 atom and Sp2 atom. These rotation angles are the angles that had been recommended by MSI Inc. as the search conditions for generating stable conformation of the compound.

Results of the analysis

**[0482]** As a result of the conformation search, it was assessed for Compound B that the 4-aminopyridine moiety which is the basic moiety of the Compound B is capable of bonding to the S3 pocket, and the binding conditions of the Compound B to the FXa satisfied all items of the aspect "17-b". It was assessed for Compound C that the 4-aminopyridine moiety which is the basic moiety of the Compound C was also capable of bonding to the S3 pocket, and the binding conditions of the Compound C to the FXa also satisfied all items of the aspect "17-b".

Measurement of the activity

**[0483]** When the activity was evaluated by the bioassay procedure described in Experimental Example 1, a) of the present invention, Compound B exhibited IC<sub>50</sub> of 0.031 mM, and Compound C exhibited IC<sub>50</sub> of 0.028 mM.

**[0484]** The pharmacophore of the present invention has been derived on the basis of the novel tricyclic compound having spiro union. This compound has played an important role in finding the novel pharmacophore which has never been reported for FXa since the three-dimensional arrangement of the three rings is fixed in this compound. Unexpectedly, it has also been confirmed that the thus derived pharmacophore is quite important and fully applicable by molecular designing means to a compound which does not have such skeleton, and in particular, to a compound having



a flexible three-dimensional arrangement.

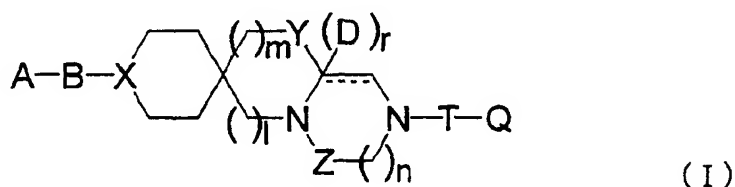
#### Industrial Applicability

**[0485]** The compound of the present invention specifically inhibits FXa, and exhibits strong anticoagulation action. The compound of the present invention is also easy to use since it exhibits high oral absorbability as well as long-lasting action and high safety. Accordingly, the compound of the present invention is very useful as an anticoagulant.

**[0486]** Furthermore, the pharmacophore of the present invention derived from the compound of the present invention is capable of providing information useful in identifying or designing the inhibitors which competitively bind to the active site of the FXa or its fragment.

#### Claims

1. A compound represented by formula (I) or its pharmaceutically acceptable salt



wherein A is a hydrogen atom, or

a group selected from (1) a saturated or unsaturated five- or six-membered cyclic hydrocarbon group, or a saturated or unsaturated five- or six-membered heterocyclic group, (2) an amino group, and (3) an imidoyl group (wherein the groups of (1) to (3) are optionally substituted);

B is a single bond, a carbonyl group,  $-S(O)_x-$ , or an optionally substituted  $C_{1-2}$  alkylene group;

D is a hydrogen atom,  $-CO-R_5$  (wherein  $R_5$  is a hydrogen atom or a substituent), or an optionally substituted  $C_{1-6}$  alkyl group;

X is a nitrogen atom or a methine group optionally substituted with a group  $A'-B'$  (wherein  $A'$  represents a group selected from those defined for A, and  $B'$  represents a group selected from those defined for B);

Y is an oxygen atom,  $-S(O)_y-$ , or an optionally substituted imino group ( $-NH-$ );

Z is a methylene group, a carbonyl group, or a thiocarbonyl group;

T is  $-S(O)_z-$ , a carbonyl group, or an optionally substituted  $C_{1-2}$  alkylene group;

Q is a hydrocarbon group or a heterocyclic group, which are optionally substituted;

l, m, n, x, y, and z are independently an integer selected from 0, 1 and 2 with the proviso that l and m are not simultaneously 0; and r is an integer of 0 or 1; and

the three rings (the ring containing X, the ring containing Y, and the ring containing Z) are independently optionally substituted; and the bond indicated by the broken line and the solid line in the ring containing Z is a single bond or a double bond (when r is 0).

2. At least one compound selected from the compounds as described below, or its (+) or (-) optical isomer, or its pharmaceutically acceptable salt:

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(hydroxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylmethoxymethyl)-7-oxa-1'-(4-pyridyl) spiro [bicyclo [4.3.0]nonane-8,4'-piperidin]-2-one;

6-(acetoxymethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

5 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyrimidinyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-((E)-4-chlorostyrylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

10 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one methanesulfone;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

15 (-) 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(isopropoxycarbonyl)-7-oxa-1'-(4-pyridyl) spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-6-(propoxycarbonyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

20 (-)-6-(allyloxycarbonyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

(-)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(2-methoxyethoxycarbonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

(-)-1,4-diaza-6-(t-butoxycarbonyl)-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

25 ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;

(+)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;

30 (-)-ammonium 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidine]-6-carboxylate;

4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-2-oxospiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-1'-yl]pyridine 1-oxide;

1'-acetimidoyl-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxaspiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

35 6-(aminomethyl)-1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(ethoxycarbonylaminomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

40 1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(morpholinomethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-methyl-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

ammonium 4-[1,4-diaza-4-(6-chloronaphthalen-2-ylsulfonyl)-7-oxa-2-oxo-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-6-yl]butylate;

45 1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-7-methyl-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4,7-triaza-4-(6-chloronaphthalen-2-ylsulfonyl)-6-(methoxymethyl)-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

50 1,4-diaza-4-(7-chloro-2H-benzopyran-3-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(7-chloro-2H-benzopyran-3-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

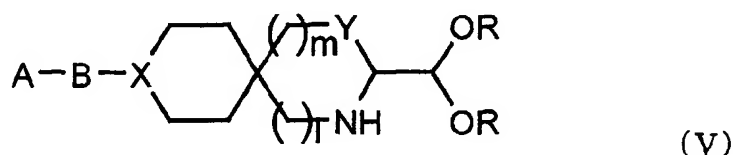
1,4-diaza-4-(6-chlorobenzothiophen-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

55 1,4-diaza-4-(6-chlorobenzothiophen-2-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]nonane-8,4'-piperidin]-2-one;

1,4-diaza-4-(5-chlorobenzofuran-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]non-

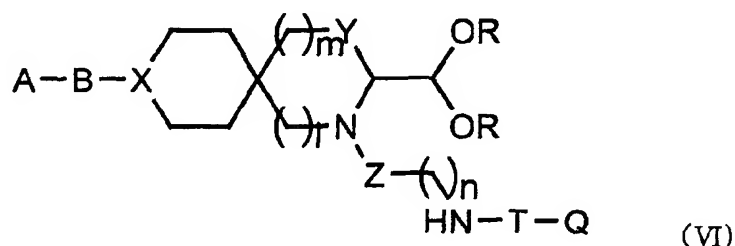
ane-8,4'-piperidin]-2-one;  
 1,4-diaza-4-(5-chlorobenzofuran-2-ylmethyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]non-  
 ane-8,4'-piperidin]-2-one, and  
 1,4-diaza-4-(6-chlorobenzofuran-2-ylsulfonyl)-(6-methoxymethyl)-7-oxa-1'-(4-pyridyl)spiro[bicyclo[4.3.0]non-  
 ane-8,4'-piperidin]-2-one.

3. A prodrug of the compound of claim 1 or 2 or its pharmaceutically acceptable salt.
4. A pharmaceutical composition **characterized by** that the composition contains a compound represented by formula (I) or its pharmaceutically acceptable salt as an effective component.
5. A FXa inhibitor **characterized by** that the inhibitor contains a compound represented by formula (I) or its pharmaceutically acceptable salt as an effective component.
6. A compound represented by formula (V) or its salt



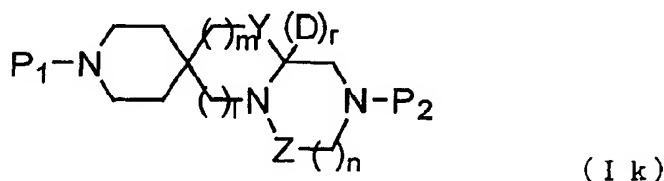
wherein A, B, X, Y, I, and m are as defined for the formula (I); the ring containing X and the ring containing Y are independently optionally substituted; and R is hydrogen atom, a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, or a C<sub>1-6</sub> alkyl group optionally substituted with hydroxyl or a halogen atom, with the proviso that two R may together form a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, a C<sub>2-4</sub> alkylene group optionally substituted with hydroxyl or a halogen atom.

7. A compound represented by formula (VI) or its salt



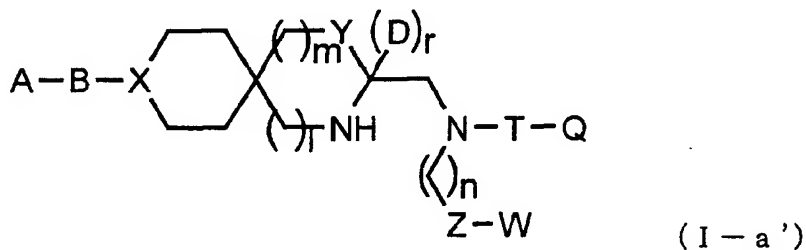
wherein A, B, X, Y, Z, T, Q, I, m, and n are as defined for the formula (I); the ring containing X and the ring containing Y are independently optionally substituted; the alkylene chain which binds to Z when n is 1 or more is optionally substituted; and R is hydrogen atom, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, a C<sub>1-6</sub> alkyl group optionally substituted with hydroxyl or a halogen atom, with the proviso that two R may together form a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> alkoxy, a C<sub>2-4</sub> alkylene group optionally substituted with hydroxyl or a halogen atom.

8. A compound represented by formula (Ik) or its salt



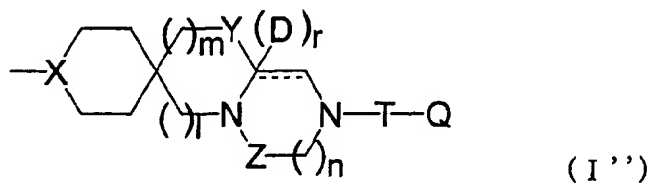
wherein  $P_1$  and  $P_2$  independently represent hydrogen atom or a protective group for the imino group; Y, Z, D, I, m, n, and r are as defined for the formula (I); and the three rings are independently optionally substituted.

9. A compound represented by formula (I-a') or its salt



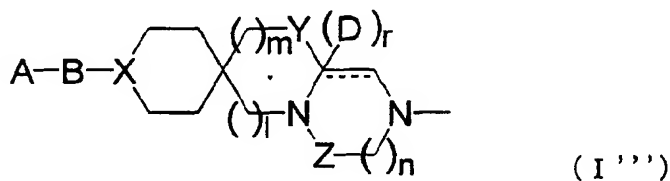
wherein A, B, D, X, Y, Z, Q, T, I, m, n, and r are as defined for the formula (I); W is a leaving group or a group convertible to a leaving group; the ring containing X and the ring containing Y are independently optionally substituted; and the alkylene which binds to Z when n is 1 or more is optionally substituted.

10. A compound exhibiting inhibitory activity for FXa which has a partial structure represented by formula (I'') in its molecule, or its pharmaceutically acceptable salt



wherein -X= is -CH= or -N=; the three rings (the ring containing X, the ring containing Y, and the ring containing Z) are independently optionally substituted; Y, Z, D, T, Q, I, m, n, and r are as defined for the formula (I).

11. A compound exhibiting inhibitory activity for FXa which has a partial structure represented by formula (I''') in its molecule, or its pharmaceutically acceptable salt



wherein X is a methine group or a nitrogen atom; the three rings (the ring containing X, the ring containing Y, and the ring containing Z) are independently optionally substituted; A, B, Y, Z, D, I, m, n, and r are as defined for formula (I).

12. A compound exhibiting inhibitory activity for FXa represented by the following formula (I'), or its pharmaceutically acceptable salt



15

20

25

35

40

45

50

55

18. A method for identifying or designing an inhibitor which competitively binds to an active site of FXa or its fragment, wherein the inhibitor is screened by providing three-dimensional structural information of the active site to a computer system; identifying a compound which is assumed to bind to the FXa in a manner satisfying all of the conditions that:

5

- (a) the compound associates with S1 pocket by its hydrophobic moiety and the moiety interacts with Tyr228,
- (b) the compound associates with the inside of S3 pocket of the active site by its basic moiety, and
- (c) the compound does not bind covalently with Ser195; and

10

subjecting the compound to a biological assay which is capable of measuring FXa inhibitory activity to thereby determine whether the compound exhibits FXa inhibitory activity in the assay.

15

20

25

30

35

40

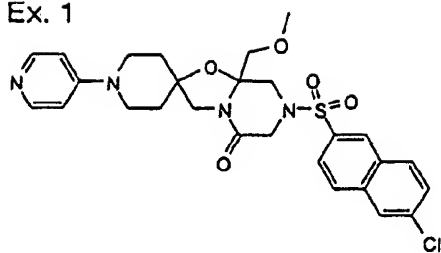
45

50

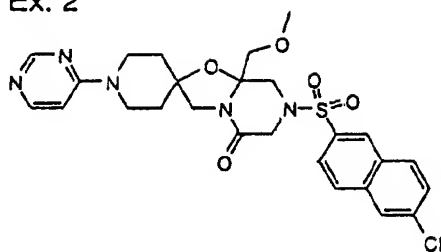
55

FIG. 1

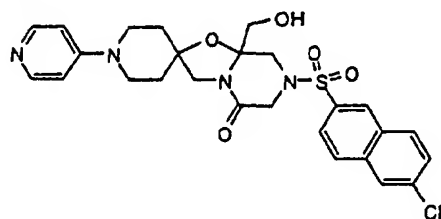
Ex. 1



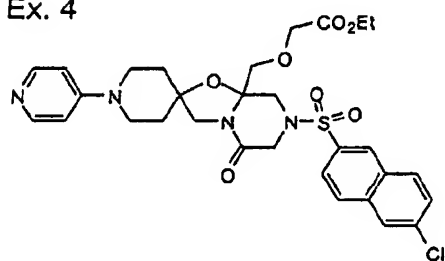
Ex. 2



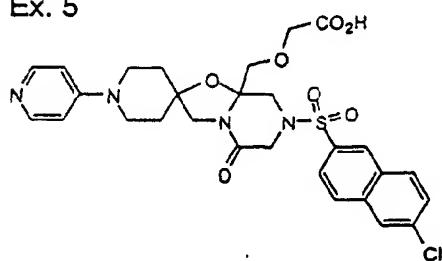
Ex. 3



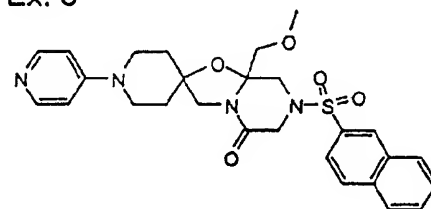
Ex. 4



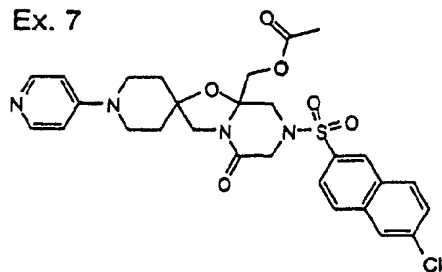
Ex. 5



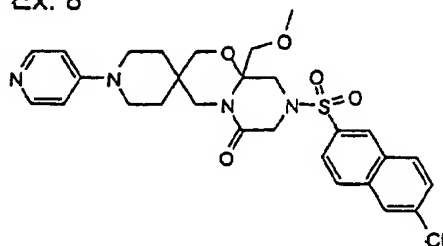
Ex. 6



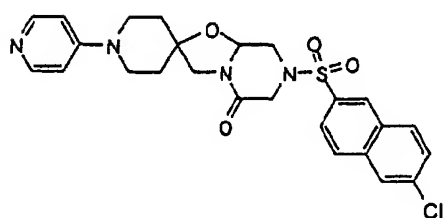
Ex. 7



Ex. 8



Ex. 9



Ex. 10

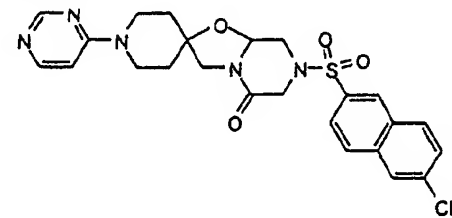
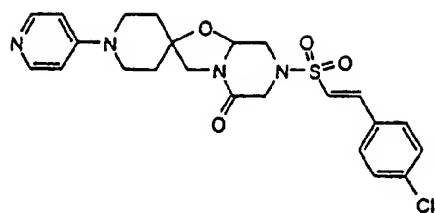
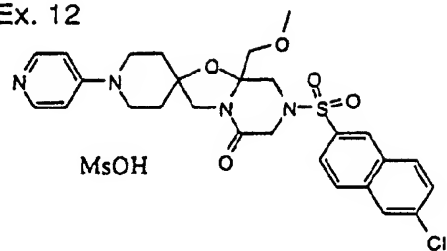


FIG. 2

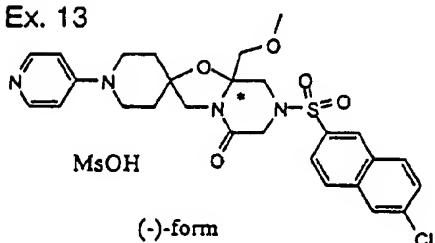
Ex. 11



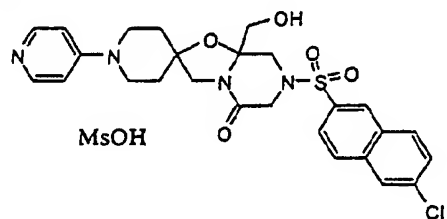
Ex. 12



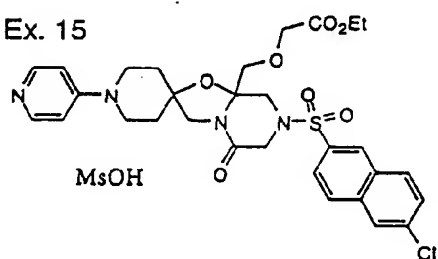
Ex. 13



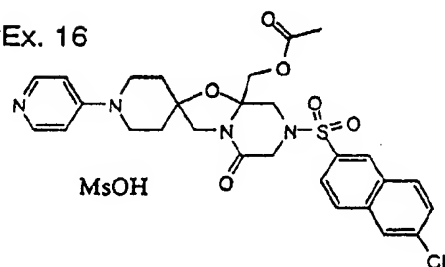
Ex. 14



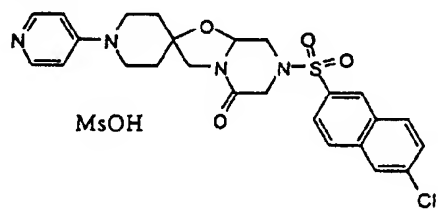
Ex. 15



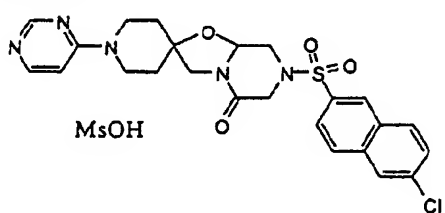
-Ex. 16



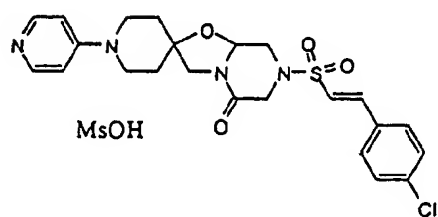
Ex. 17



Ex. 18



Ex. 19



Ex. 20

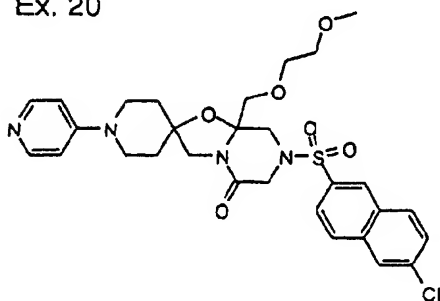
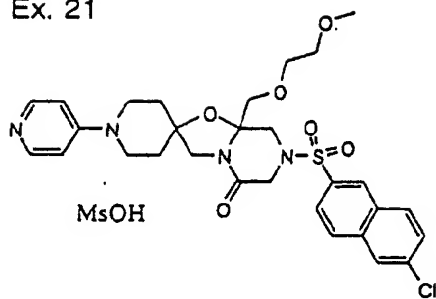


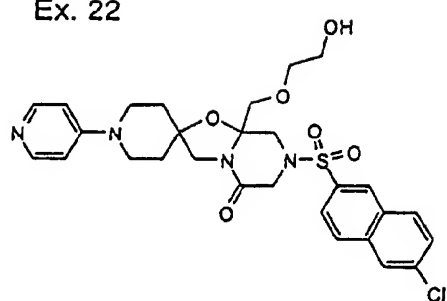


FIG. 3

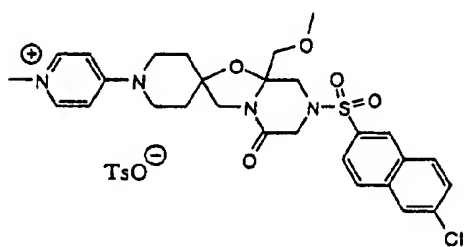
Ex. 21



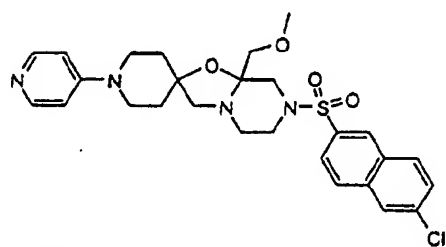
Ex. 22



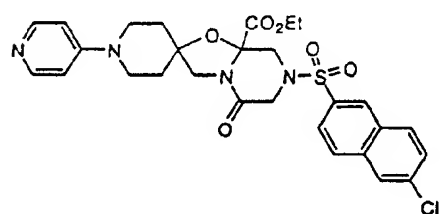
Ex. 23



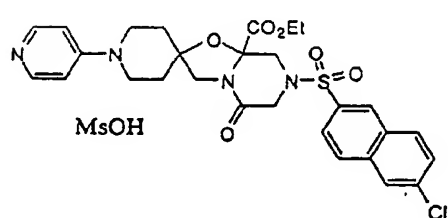
Ex. 24



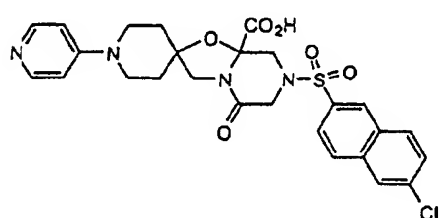
Ex. 25



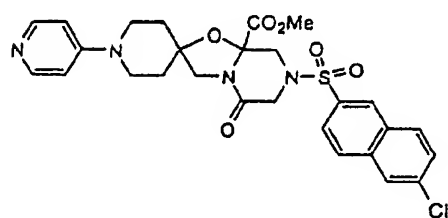
Ex. 26



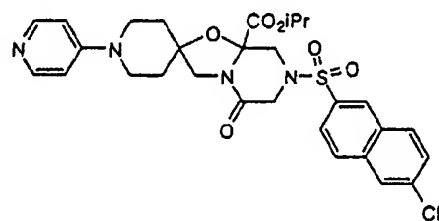
Ex. 27



Ex. 28



Ex. 29



Ex. 30

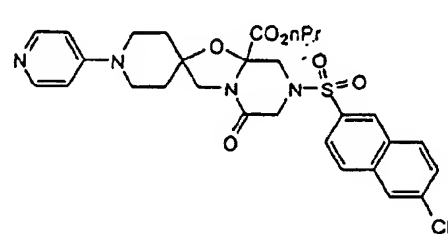
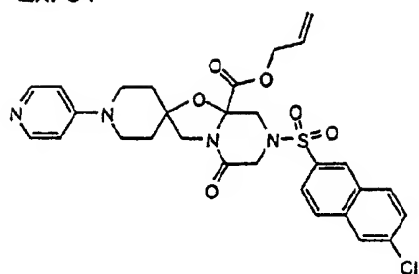
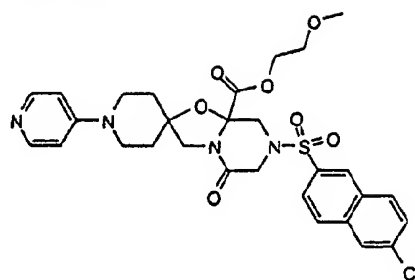


FIG. 4

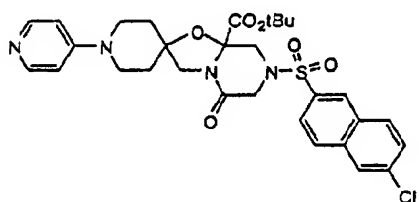
Ex. 31



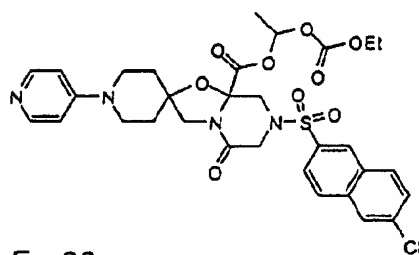
Ex. 32



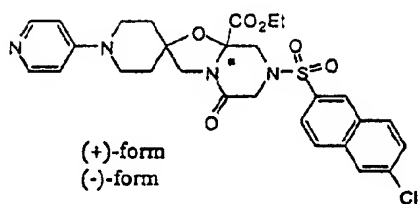
Ex. 33



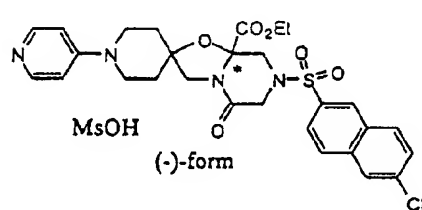
Ex. 34



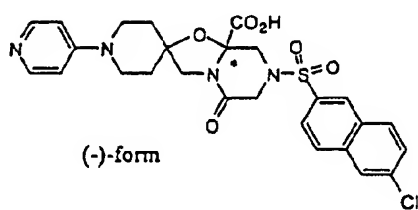
Ex. 35



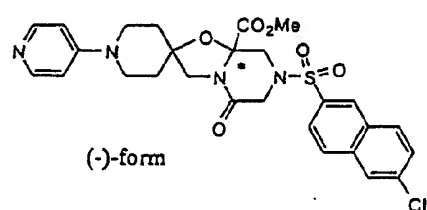
Ex. 36



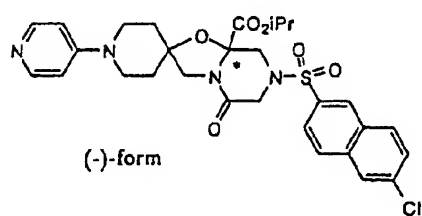
Ex. 37



Ex. 38



Ex. 39



Ex. 40

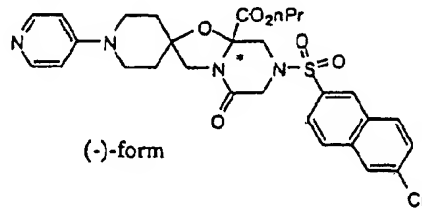
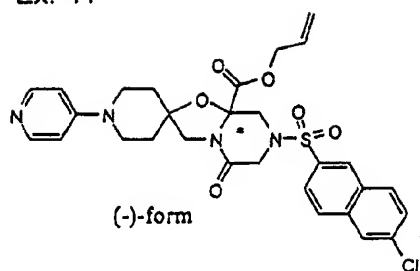
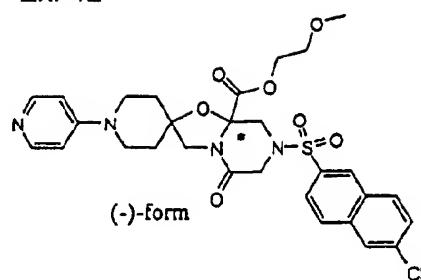


FIG. 5

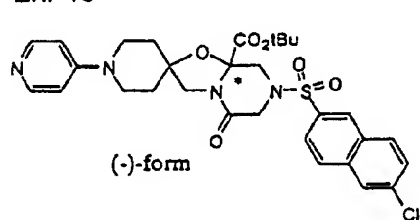
Ex. 41



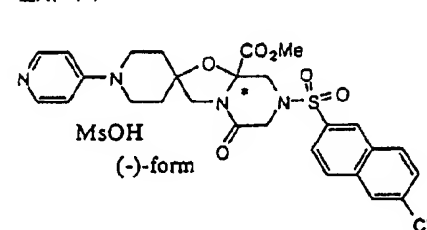
Ex. 42



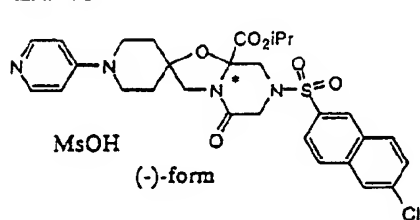
Ex. 43



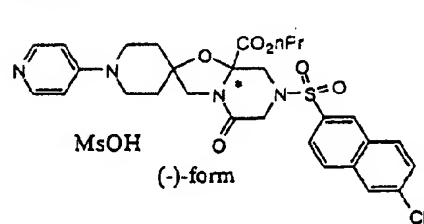
Ex. 44



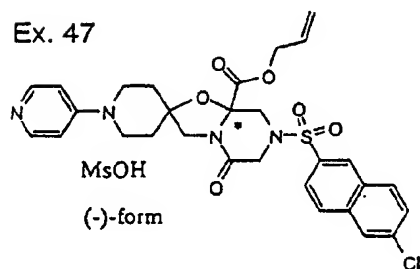
Ex. 45



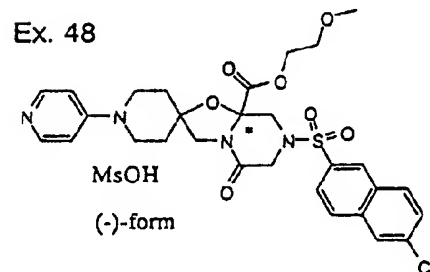
Ex. 46



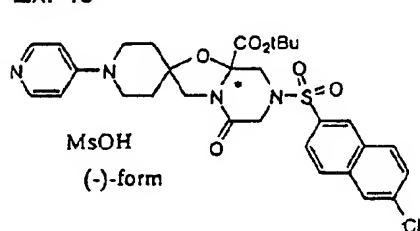
Ex. 47



Ex. 48



Ex. 49



Ex. 50

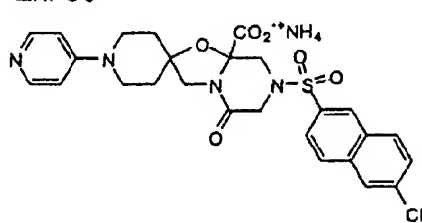
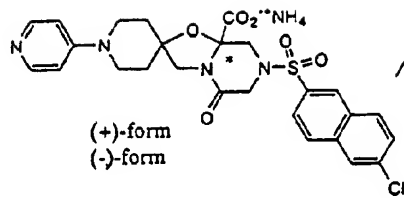
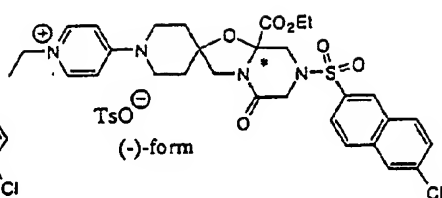


FIG. 6

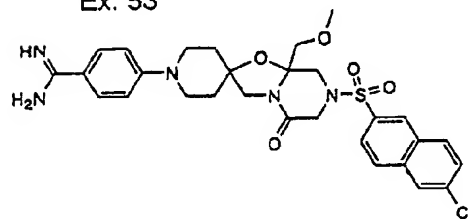
Ex. 51



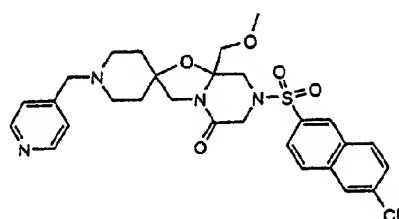
Ex. 52



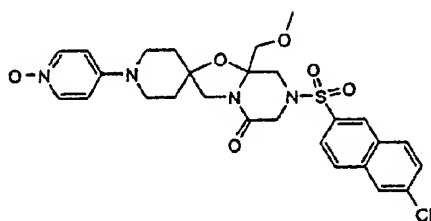
Ex. 53



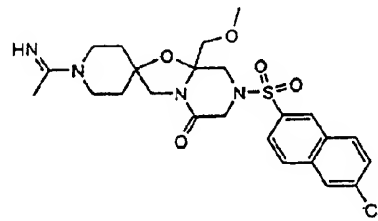
Ex. 54



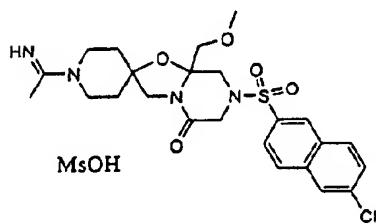
Ex. 55



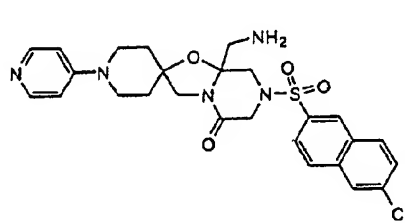
Ex. 56



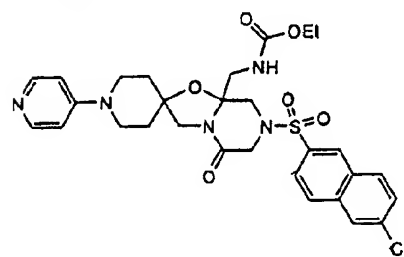
Ex. 57



Ex. 58



Ex. 59



Ex. 60

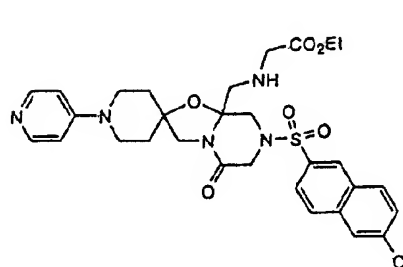


FIG. 7

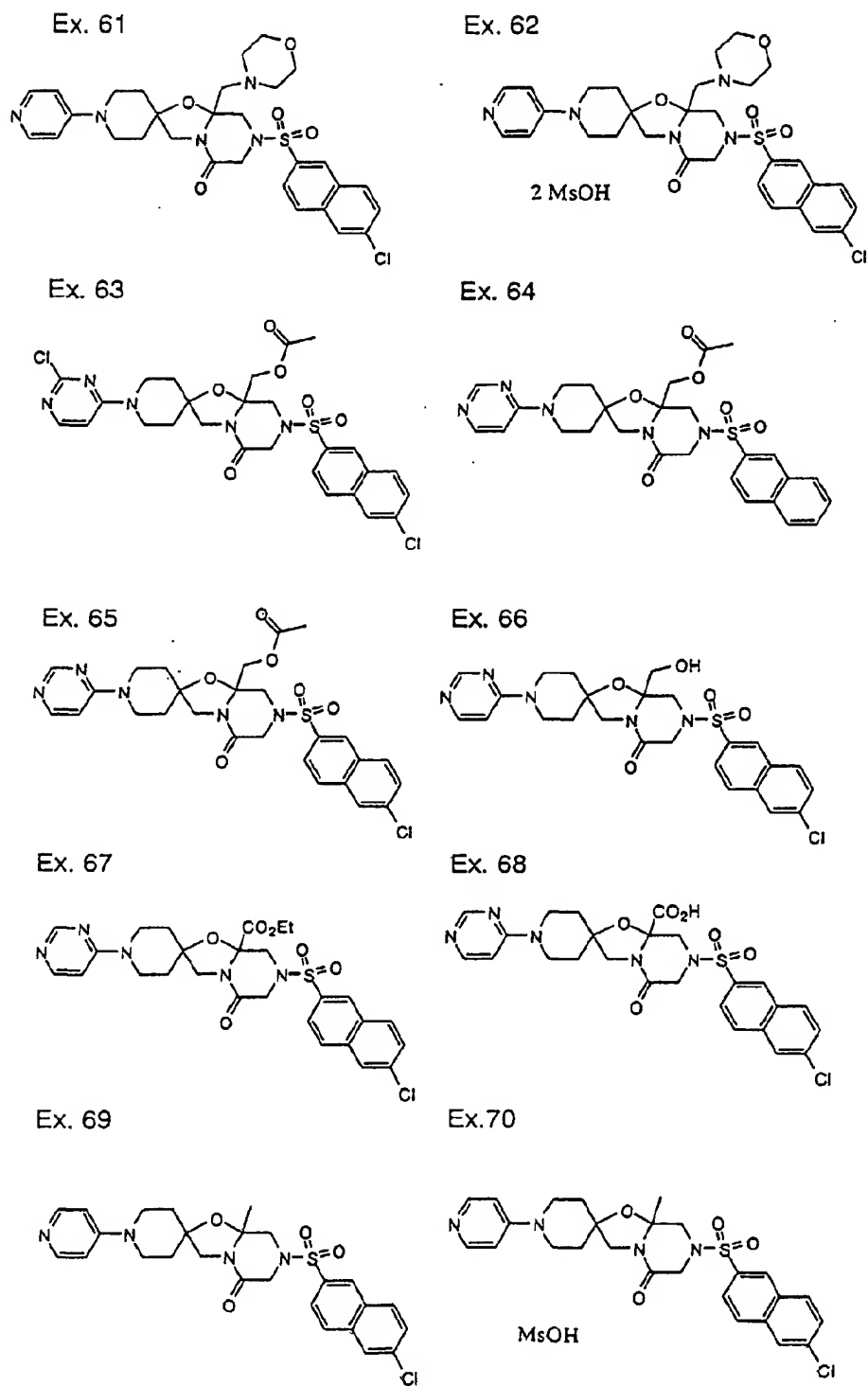
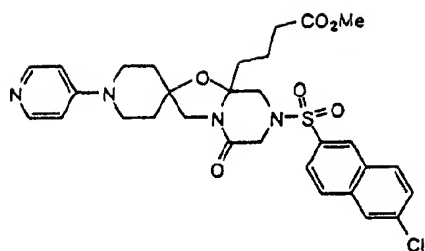
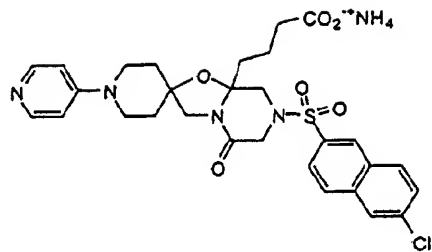


FIG. 8

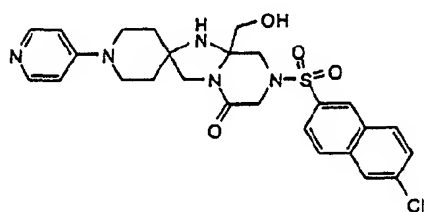
Ex. 71



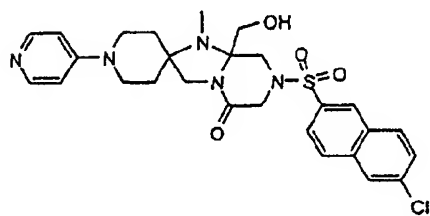
Ex. 72



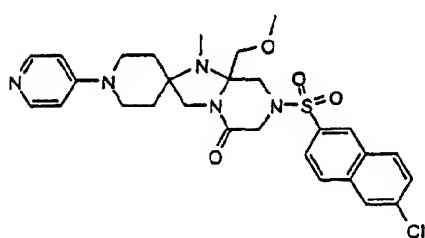
Ex. 73



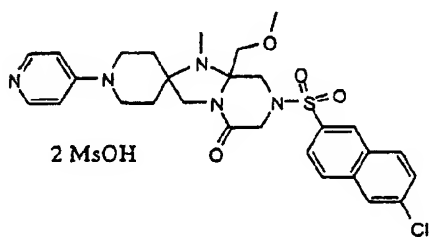
Ex. 74



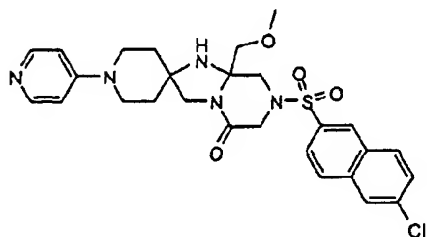
Ex. 75



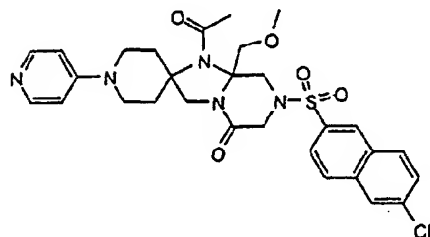
Ex. 76



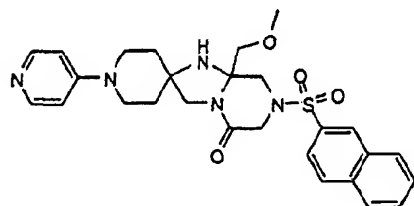
Ex. 77



Ex. 78



Ex. 79



Ex. 80

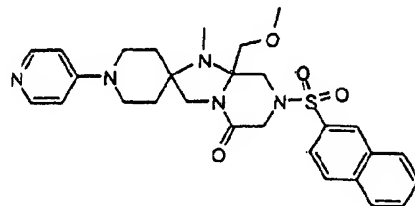
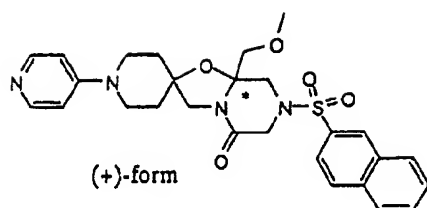


FIG. 9

Ex. 81



Ex. 82

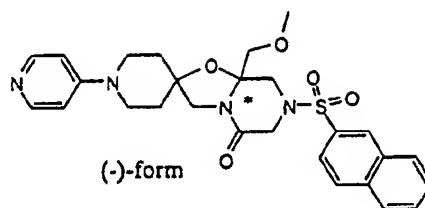
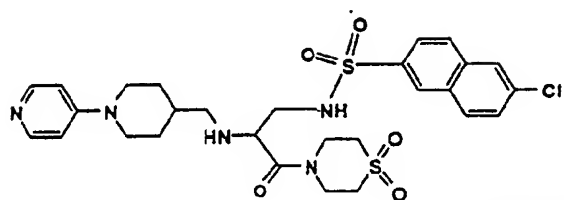
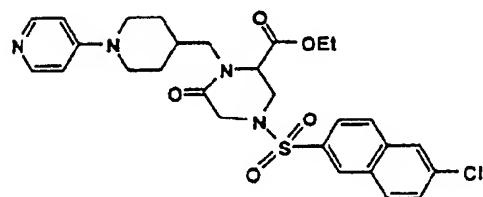


FIG. 10



Compound B



Compound C

FIG. 11

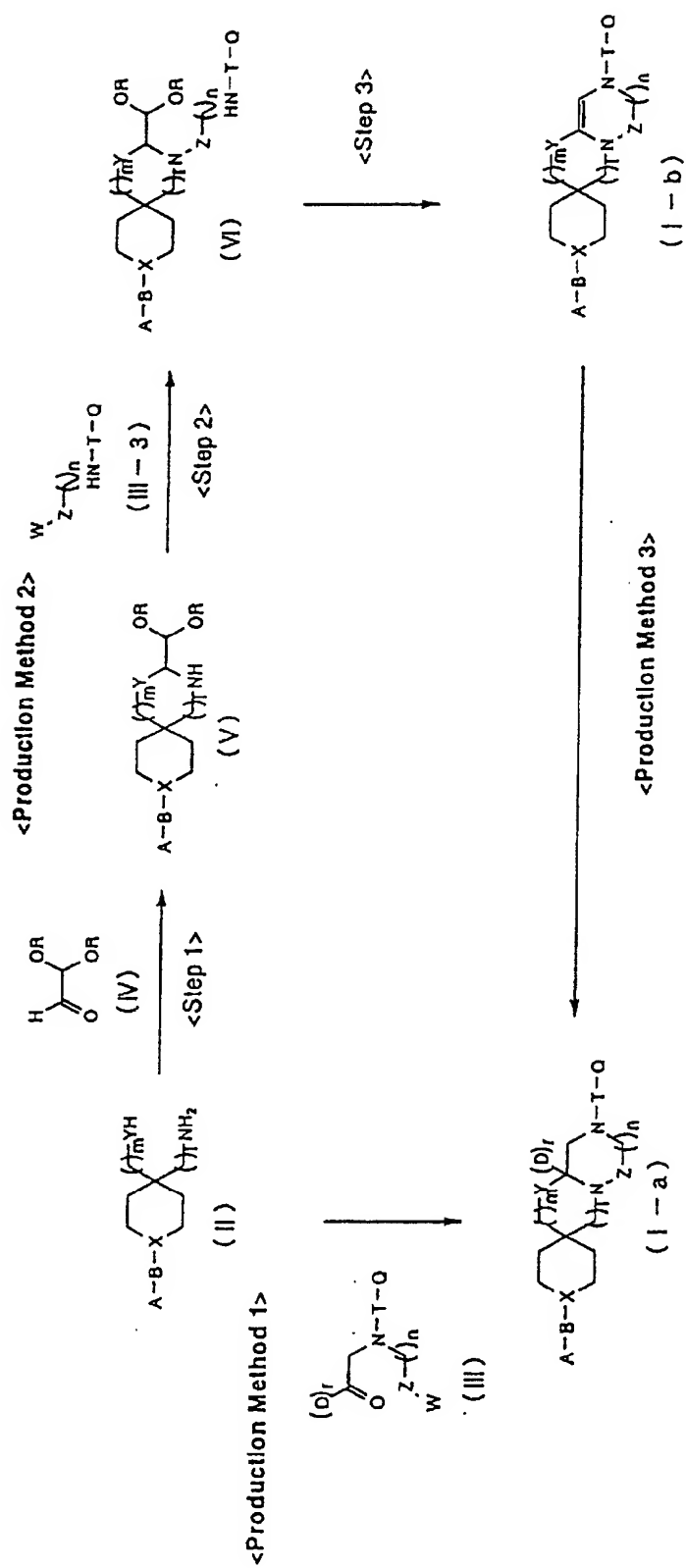




FIG. 12

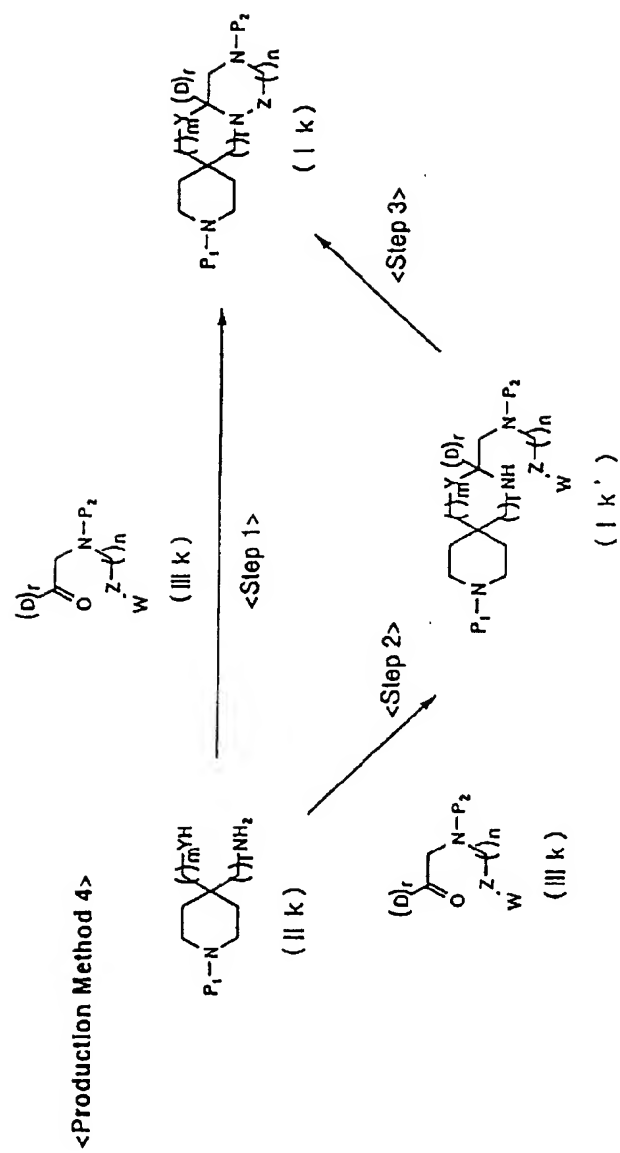


FIG. 13

&lt;Production Method 1&gt;

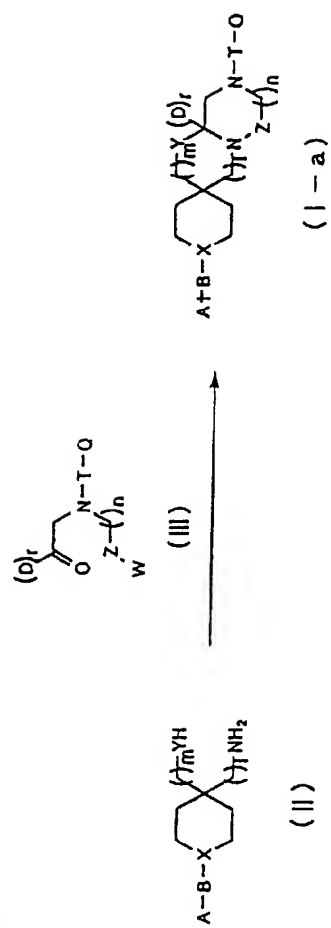
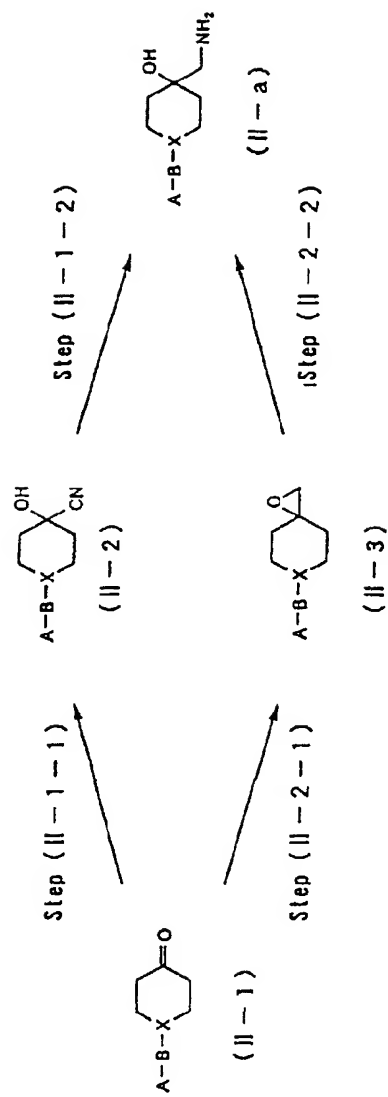
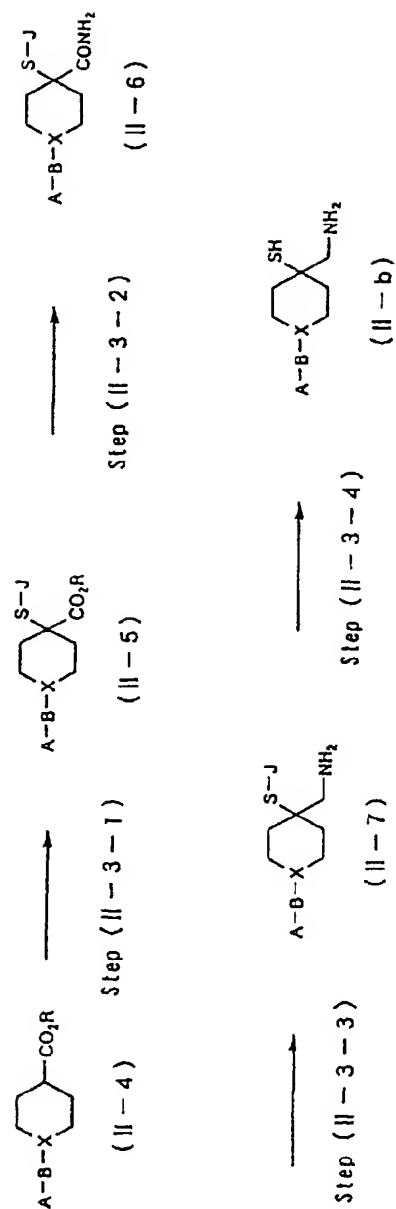


FIG. 14

&lt;Production Method 1&gt;

Production Method of (II)

 $1-f)/=1, m=0$  $Y=O$  $Y=S$ 

## &lt;Production Method 1&gt;

## Production Method of (II)

1-2)  $l=0,1,2$ ,  $m=1,2$   
 $Y=O$ 

FIG. 15

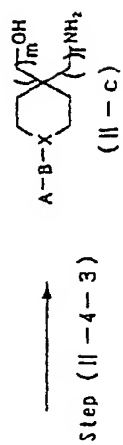
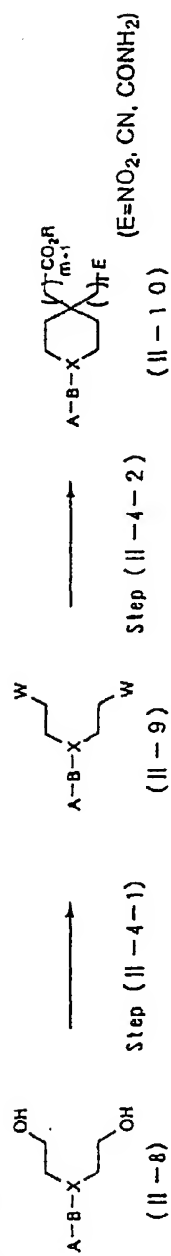
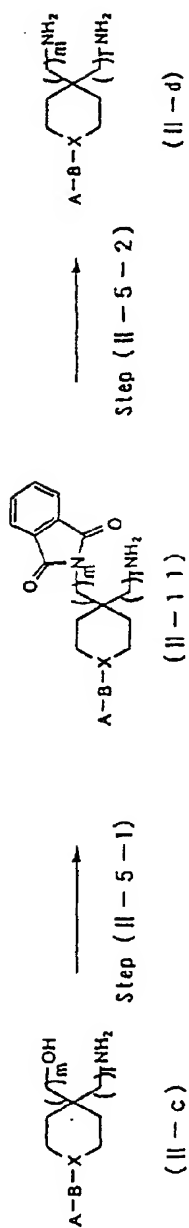
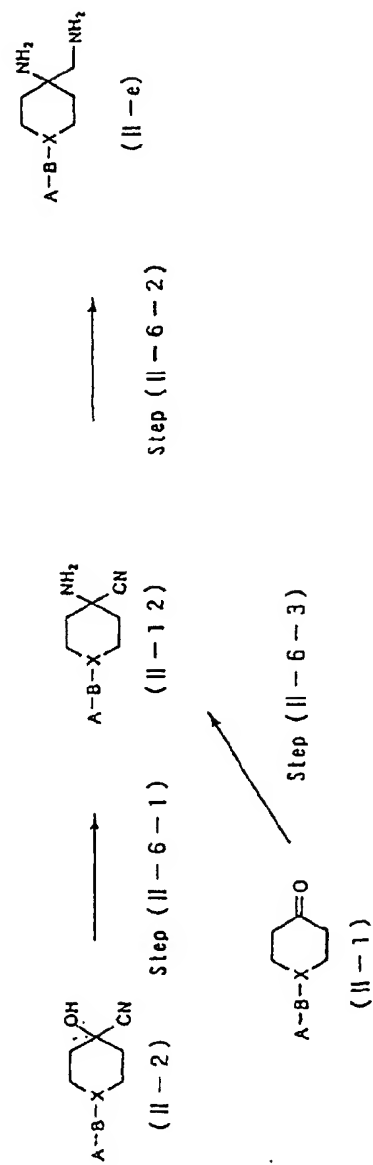
 $Y=N$  $Y=N$ 

FIG.16

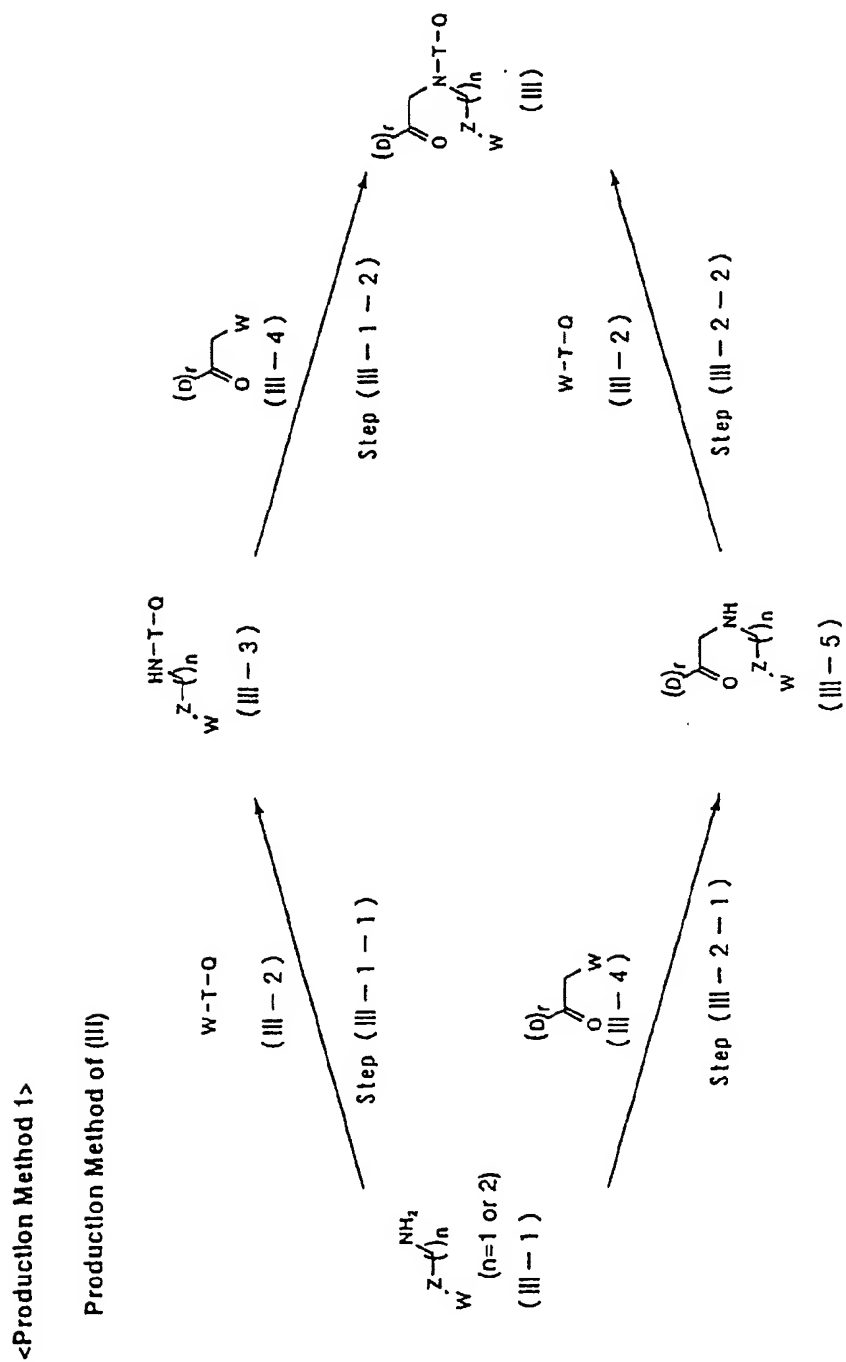


FIG. 17

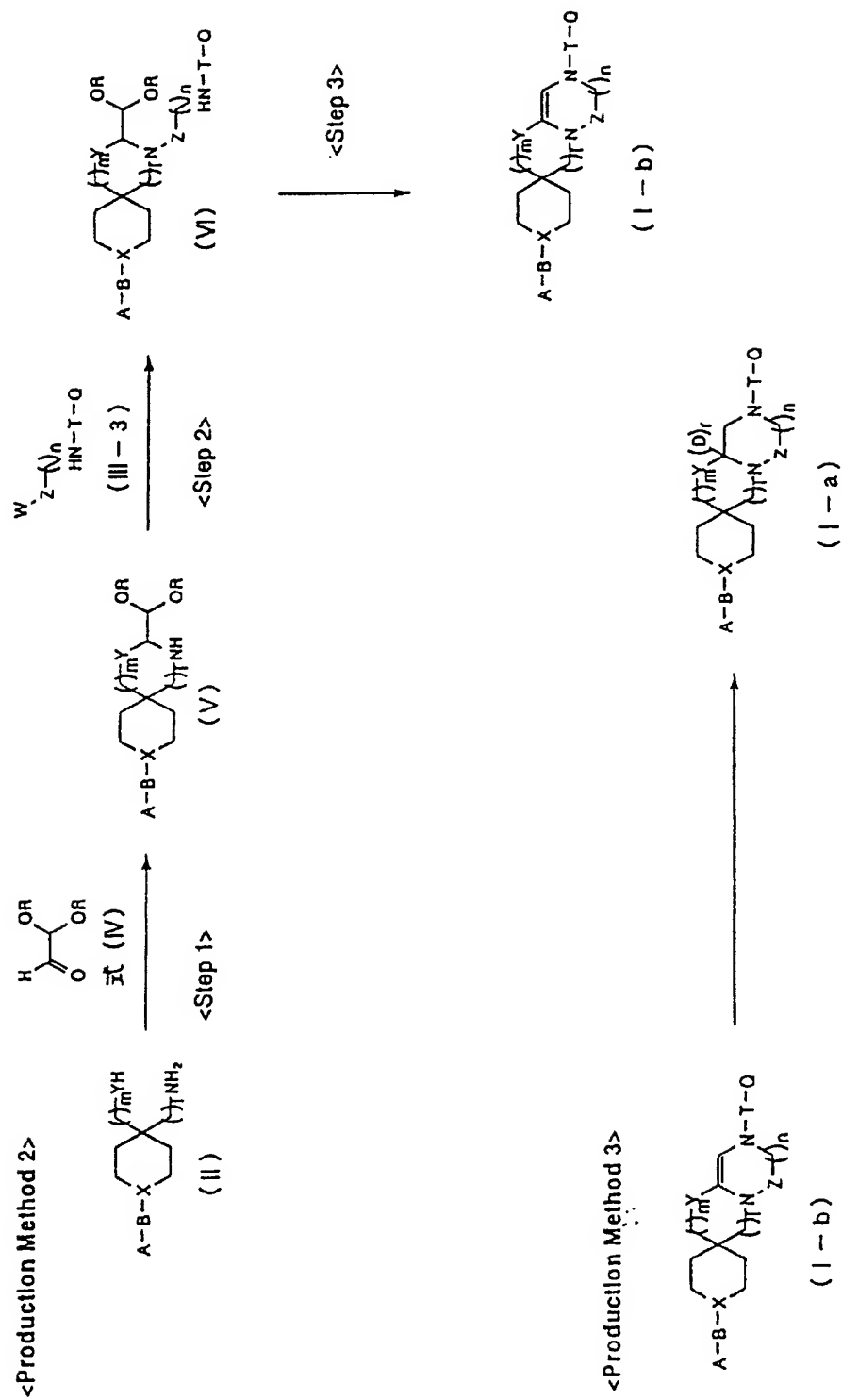
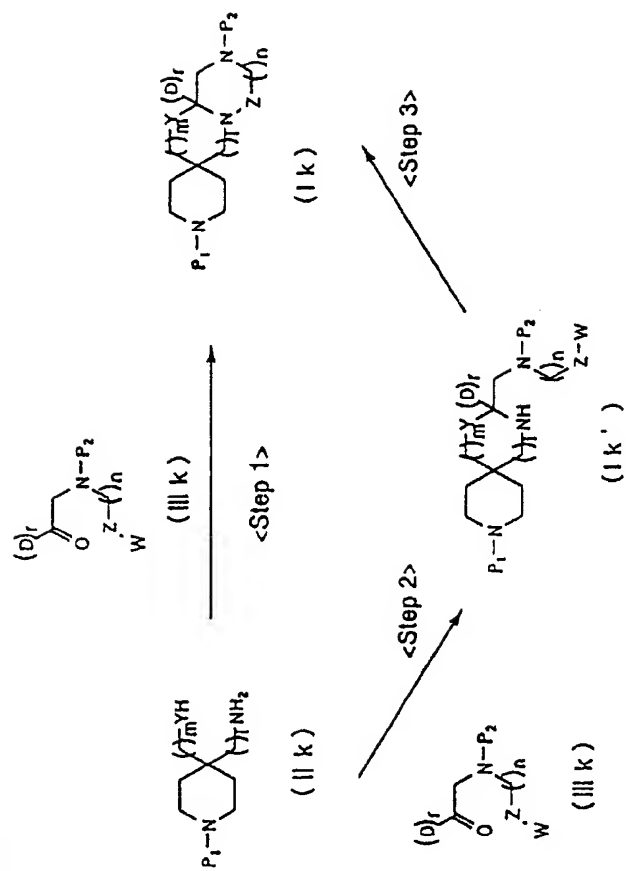


FIG. 18

&lt;Production Method 4&gt;

X=N



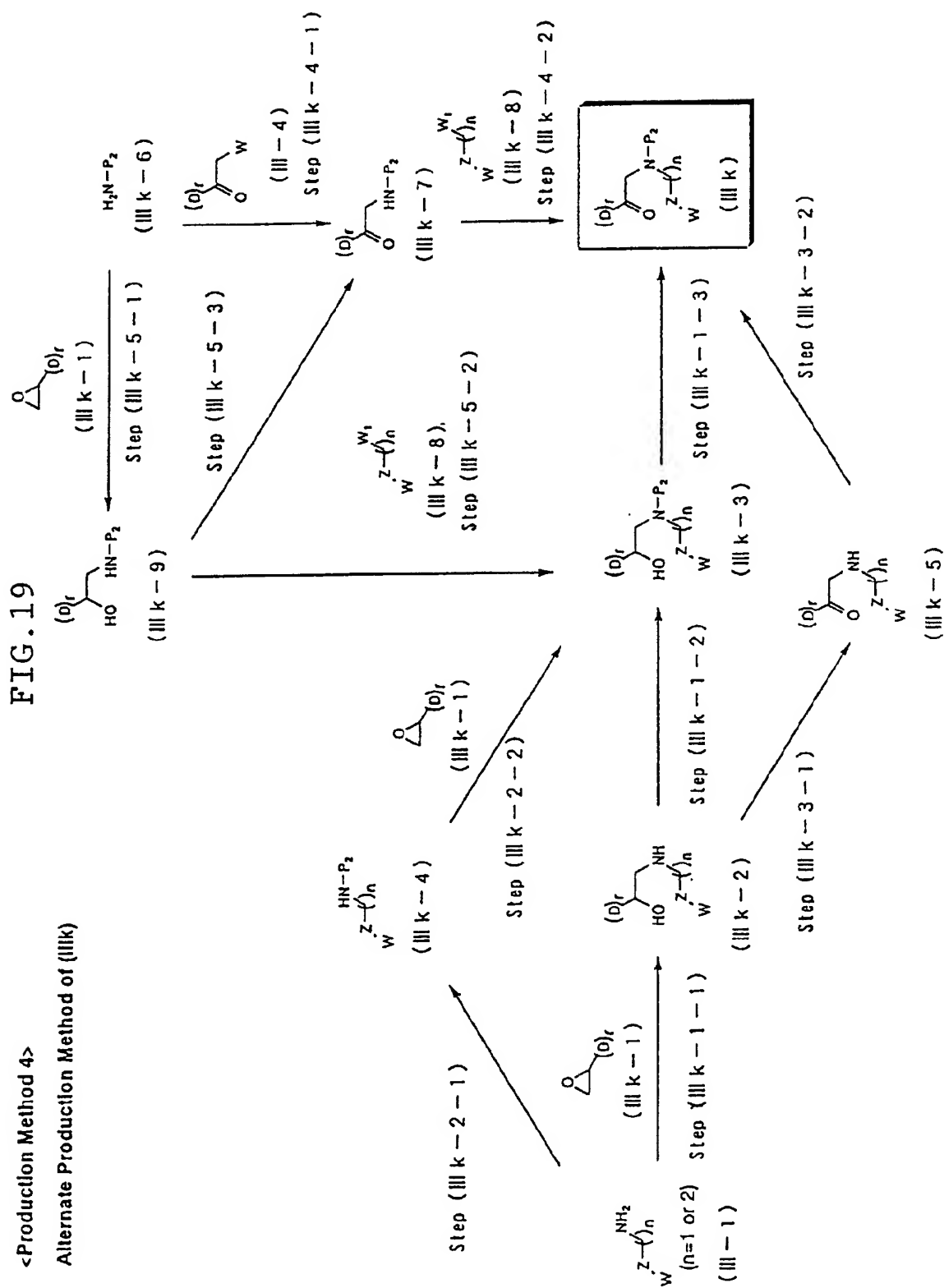




FIG. 20

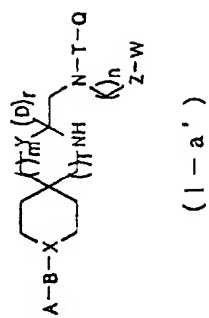
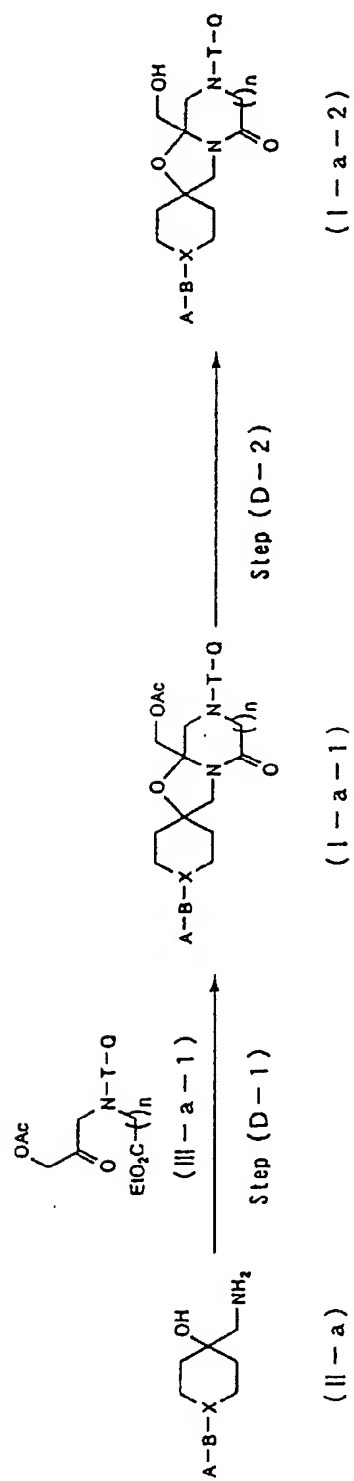
<Converted Example of D (-CH<sub>2</sub>OH)>

FIG. 21

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
1	CDCl <sub>3</sub> : 8.38-8.33 (1H, m), 8.27-8.20 (2H, m), 7.99-7.92 (3H, m), 7.79 (1H, dd, J=2, 9Hz), 7.65-7.59 (1H, m), 6.66-6.58 (2H, m), 4.42-4.32 (2H, m), 4.25-4.17 (1H, m), 3.71-3.58 (2H, m), 3.53-3.17 (5H, m), 3.43 (3H, s), 3.35 (1H, d, J=17Hz), 2.30 (1H, d, J=12Hz), 2.03-1.80 (2H, m), 1.57-1.45 (2H, m)
2	CDCl <sub>3</sub> : 8.56 (1H, s), 8.38-8.33 (1H, m), 8.18 (1H, d, J=6Hz), 7.99-7.92 (3H, m), 7.82-7.76 (1H, m), 7.65-7.58 (1H, m), 6.50-6.45 (1H, m), 4.42-4.30 (2H, m), 4.20 (1H, d, J=12Hz), 3.94-3.37 (4H, m), 3.68 (1H, d, J=10Hz), 3.63 (1H, d, J=10Hz), 3.43 (3H, s), 3.36 (1H, d, J=17Hz), 3.22 (1H, d, J=12Hz), 2.31 (1H, d, J=12Hz), 2.02-1.72 (2H, m), 1.53-1.43 (2H, m)
3	CDCl <sub>3</sub> : 8.38-8.34 (1H, m), 8.28-8.19 (2H, m), 7.98-7.92 (3H, m), 7.82-7.76 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.66-6.58 (2H, m), 4.48-4.22 (3H, m), 3.98-3.88 (1H, m), 3.80-3.69 (1H, m), 3.54-3.15 (5H, m), 3.40 (1H, d, J=17Hz), 2.33 (1H, d, J=12Hz), 2.22-1.82 (2H, m), 1.58-1.48 (2H, m)
4	CDCl <sub>3</sub> : 8.37-8.32 (1H, m), 8.28-8.21 (2H, m), 7.99-7.91 (3H, m), 7.78 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 6.65-6.58 (2H, m), 4.42-4.10 (7H, m), 3.92 (1H, d, J=10Hz), 3.80 (1H, d, J=10Hz), 3.57-3.16 (6H, m), 2.32 (1H, d, J=12Hz), 2.17-2.06 (1H, m), 1.96-1.83 (1H, m), 1.56-1.47 (2H, m), 1.35-1.20 (3H, m)
5	CD <sub>3</sub> OD: 8.53-8.47 (1H, m), 8.18-8.03 (5H, m), 7.92-7.83 (1H, m), 7.68-7.62 (1H, m), 7.18-7.09 (2H, m), 4.34 (1H, d, J=12Hz), 4.35-4.20 (1H, m), 4.20-3.26 (11H, m), 2.65 (1H, d, J=12Hz), 2.22-2.10 (1H, m), 2.02-1.88 (1H, m), 1.73-1.55 (2H, m)
6	CDCl <sub>3</sub> : 8.40-8.37 (1H, m), 8.28-8.20 (2H, m), 8.07-7.93 (3H, m), 7.80-7.64 (3H, m), 6.66-6.58 (2H, m), 4.42-4.30 (2H, m), 4.20 (1H, d, J=12Hz), 3.72-3.61 (2H, m), 3.52-3.18 (4H, m), 3.44 (3H, s), 3.35 (1H, d, J=17Hz), 3.21 (1H, d, J=12Hz), 2.28 (1H, d, J=12Hz), 2.04-1.79 (2H, m), 1.57-1.45 (2H, m)
7	CDCl <sub>3</sub> : 8.40-8.36 (1H, m), 8.29-8.20 (2H, m), 8.00-7.94 (3H, m), 7.80 (1H, dd, J=2, 9Hz), 7.63 (1H, dd, J=2, 9Hz), 6.66-6.59 (2H, m), 4.54-4.15 (5H, m), 3.60-3.14 (6H, m), 2.36 (1H, d, J=12Hz), 2.13 (3H, s), 1.99-1.73 (2H, m), 1.62-1.46 (2H, m)

FIG. 22

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
8	CDCl <sub>3</sub> : 8.37-8.34 (1H, m), 8.26-8.19 (2H, m), 7.99-7.91 (3H, m), 7.79 (1H, dd, J=2, 9Hz), 7.65-7.59 (1H, m), 6.62-6.55 (2H, m), 4.72 (1H, dd, J=2, 14Hz), 4.35-4.25 (2H, m), 4.07 (1H, d, J=11Hz), 3.74 (1H, d, J=12Hz), 3.63 (1H, d, J=11Hz), 3.49 (3H, s), 3.34 (1H, d, J=17Hz), 3.63-3.28 (3H, m), 3.26-3.11 (2H, m), 2.68 (1H, d, J=14Hz), 2.42 (1H, d, J=12Hz), 1.68-1.40 (4H, m)
9	CDCl <sub>3</sub> : 8.45-8.13 (3H, m), 8.00-7.90 (3H, m), 7.79 (1H, dd, J=2, 8Hz), 7.62 (1H, dd, J=2, 9Hz), 6.82-6.58 (2H, m), 5.26-5.18 (1H, m), 4.45-4.26 (2H, m), 3.77 (1H, d, J=12Hz), 3.70-3.51 (2H, m), 3.47-3.23 (2H, m), 3.32 (1H, d, J=17Hz), 3.19 (1H, d, J=12Hz), 2.52-2.39 (1H, m), 2.06-1.88 (1H, m), 1.85-1.59 (3H, m)
10	CDCl <sub>3</sub> : 8.59 (1H, s), 8.40-8.35 (1H, m), 8.20 (1H, d, J=6Hz), 8.04-7.87 (3H, m), 7.80 (1H, dd, J=2, 9Hz), 7.61 (1H, dd, J=2, 9Hz), 6.52 (1H, d, J=6Hz), 5.27-5.18 (1H, m), 4.45-4.28 (2H, m), 4.12-3.94 (2H, m), 3.81-3.71 (1H, m), 3.55-3.32 (2H, m), 3.32 (1H, d, J=17Hz), 3.23-3.15 (1H, m), 2.46 (1H, dd, J=9, 12Hz), 2.01-1.88 (1H, m), 1.79-1.60 (3H, m)
11	CDCl <sub>3</sub> : 8.31-8.25 (2H, m), 7.50 (1H, d, J=15Hz), 7.49-7.38 (4H, m), 6.72-6.60 (3H, m), 5.23-5.17 (1H, m), 4.33-4.22 (2H, m), 3.87-3.80 (1H, m), 3.65-3.51 (2H, m), 3.59 (1H, d, J=17Hz), 3.44-3.27 (2H, m), 3.25-3.19 (1H, m), 2.78-2.69 (1H, m), 2.02-1.92 (1H, m), 1.88-1.69 (3H, m)
12	CDCl <sub>3</sub> : 14.2 (1H, brs), 8.40-8.33 (1H, m), 8.28-8.15 (2H, m), 8.02-7.92 (3H, m), 7.83-7.75 (1H, m), 7.67-7.58 (1H, m), 6.94-6.82 (2H, m), 4.45-4.26 (2H, m), 4.26-4.13 (1H, m), 3.96-3.23 (8H, m), 3.43 (3H, s), 2.86 (3H, s), 2.34 (1H, d, J=12Hz), 2.18-2.04 (1H, m), 1.96-1.79 (1H, m), 1.68-1.54 (2H, m)
13	CDCl <sub>3</sub> : 14.21 (1H, brs), 8.40-8.33 (1H, m), 8.28-8.15 (2H, m), 8.02-7.92 (3H, m), 7.83-7.75 (1H, m), 7.67-7.58 (1H, m), 6.94-6.82 (2H, m), 4.45-4.26 (2H, m), 4.26-4.13 (1H, m), 3.96-3.23 (8H, m), 3.43 (3H, s), 2.86 (3H, s), 2.34 (1H, d, J=12Hz), 2.18-2.04 (1H, m), 1.96-1.79 (1H, m), 1.68-1.54 (2H, m)
14	CD <sub>3</sub> OD: 8.53-8.48 (1H, m), 8.16-8.03 (5H, m), 7.91-7.85 (1H, m), 7.66 (1H, dd, J=2, 9Hz), 7.18-7.08 (2H, m), 4.32-4.12 (3H, m), 4.08-3.96 (1H, m), 3.94-3.60 (4H, m), 3.58-3.42 (1H, m), 3.50 (1H, d, J=17Hz), 3.38-3.27 (1H, m), 2.69 (3H, s), 2.62 (1H, d, J=12Hz), 2.13-1.85 (2H, m), 1.72-1.53 (2H, m)

FIG. 23

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
15	DMSO-d <sub>6</sub> : 13.32-13.10 (1H, br), 8.61 (1H, s), 8.34-8.12 (5H, m), 7.95-7.86 (1H, m), 7.79-7.70 (1H, m), 7.24-7.14 (2H, m), 4.22-4.03 (6H, m), 3.94-2.90 (9H, m), 2.71 (1H, d, J=11Hz), 2.30 (3H, s), 1.97-1.81 (2H, m), 1.64-1.49 (2H, m), 1.26-1.16 (3H, m)
17	CDCl <sub>3</sub> : 8.40-8.35 (1H, m), 8.30-8.21 (2H, m), 8.00-7.92 (3H, m), 7.82-7.76 (1H, m), 7.65-7.59 (1H, m), 6.93-6.85 (2H, m), 5.28-5.20 (1H, m), 4.44-4.32 (1H, m), 4.33 (1H, d, J=17Hz), 4.00-3.80 (3H, m), 3.65-3.40 (2H, m), 3.34 (1H, d, J=17Hz), 3.21 (1H, d, J=12Hz), 2.85 (3H, s), 2.58-2.47 (1H, m), 2.20-1.70 (4H, m)
20	CDCl <sub>3</sub> : 8.37-8.33 (1H, m), 8.28-8.20 (2H, m), 7.98-7.92 (3H, m), 7.81-7.75 (1H, m), 7.65-7.59 (1H, m), 6.65-6.59 (2H, m), 4.40-4.28 (2H, m), 4.17 (1H, d, J=11Hz), 3.83-3.73 (2H, m), 3.72-3.66 (2H, m), 3.59-3.53 (2H, m), 3.38 (3H, s), 3.51-3.22 (6H, m), 2.31 (1H, d, J=12Hz), 2.09-1.98 (1H, m), 1.93-1.80 (1H, m), 1.54-1.46 (2H, m)
21	DMSO-d <sub>6</sub> : 13.34-13.12 (1H, br), 8.62 (1H, s), 8.34-8.25 (2H, m), 8.24-8.13 (3H, m), 7.96-7.87 (1H, m), 7.79-7.72 (1H, m), 7.24-7.16 (2H, m), 4.18-4.02 (3H, m), 3.94-3.80 (1H, m), 3.80-3.68 (1H, m), 3.26 (3H, s), 3.68-3.15 (10H, m), 2.70 (1H, d, J=11Hz), 2.30 (3H, s), 1.94-1.81 (2H, m), 1.64-1.51 (2H, m)
22	CDCl <sub>3</sub> : 8.37-8.34 (1H, m), 8.27-8.21 (2H, m), 7.99-7.92 (3H, m), 7.81-7.76 (1H, m), 7.65-7.60 (1H, m), 6.64-6.58 (2H, m), 4.55-4.48 (1H, m), 4.39 (1H, d, J=17Hz), 4.25 (1H, d, J=12Hz), 3.88 (1H, d, J=10Hz), 3.85-3.72 (3H, m), 3.72-3.60 (2H, m), 3.50-3.42 (2H, m), 3.34 (1H, d, J=17Hz), 3.42-3.23 (2H, m), 3.18 (1H, d, J=12Hz), 2.27 (1H, d, J=12Hz), 2.02-1.80 (2H, m), 1.56-1.46 (2H, m)
23	CDCl <sub>3</sub> : 8.37-8.33 (1H, m), 8.22-8.14 (2H, m), 7.99-7.92 (3H, m), 7.80-7.71 (3H, m), 7.60 (1H, dd, J=2, 9Hz), 7.15-7.07 (4H, m), 4.38-4.26 (2H, m), 4.13 (1H, d, J=12Hz), 3.96 (3H, s), 3.95-3.80 (2H, m), 3.65 (2H, s), 3.41 (3H, s), 3.63-3.35 (2H, m), 3.35 (1H, d, J=17Hz), 3.23 (1H, d, J=12), 2.35 (1H, d, J=12Hz), 2.31 (3H, s), 2.09-1.99 (1H, m), 1.90-1.76 (1H, m), 1.60-1.50 (2H, m)
24	CDCl <sub>3</sub> : 8.36-8.31 (1H, m), 8.26-8.18 (2H, m), 7.98-7.90 (3H, m), 7.81-7.75 (1H, m), 7.63-7.56 (1H, m), 6.66-6.59 (2H, m), 3.81-3.72 (1H, m), 3.63 (1H, d, J=11Hz), 3.40 (3H, s), 3.50-3.22 (7H, m), 3.10-3.01 (1H, m), 2.97-2.84 (2H, m), 2.77-2.66 (1H, m), 2.25 (1H, d, J=12Hz), 2.01-1.90 (1H, m), 1.76-1.59 (3H, m)

FIG. 24

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
25	CDCl <sub>3</sub> : 8.35 (1H, s), 8.30-8.20 (2H, m), 8.00-7.86 (3H, m), 7.82-7.71 (1H, m), 7.66-7.56 (1H, m), 6.66-6.57 (2H, m), 4.76 (1H, d, J=12Hz), 4.38-4.21 (3H, m), 4.11 (1H, d, J=12Hz), 3.54-3.23 (6H, m), 2.49 (1H, d, J=12Hz), 1.89-1.73 (2H, m), 1.73-1.52 (2H, m), 1.41-1.29 (3H, m)
26	CDCl <sub>3</sub> : 14.43 (1H, brs), 8.36 (1H, s), 8.28-8.16 (2H, m), 8.02-7.86 (3H, m), 7.82-7.73 (1H, m), 7.66-7.57 (1H, m), 6.97-6.88 (2H, m), 4.82-4.70 (1H, m), 4.40-4.21 (3H, m), 4.14 (1H, d, J=12Hz), 3.95-3.80 (2H, m), 3.66-3.29 (4H, m), 2.82 (3H, s), 2.58-2.48 (1H, m), 1.98-1.77 (2H, m), 1.77-1.63 (2H, m), 1.44-1.30 (3H, m)
27	DMSO-d <sub>6</sub> : 8.60 (1H, s), 8.30 (1H, d, J=9Hz), 8.27-8.21 (1H, m), 8.21-8.08 (3H, m), 7.94-7.84 (1H, m), 7.77-7.69 (1H, m), 6.99 (2H, d, J=7Hz), 4.48 (1H, d, J=11Hz), 3.98-3.82 (2H, m), 3.76-3.54 (2H, m), 3.54-3.17 (2H, m), 3.39 (1H, d, J=16Hz), 3.23 (1H, d, J=12Hz), 2.71 (1H, d, J=11Hz), 1.79-1.64 (2H, m), 1.64-1.47 (2H, m)
28	CDCl <sub>3</sub> : 8.42-8.32 (1H, m), 8.31-8.18 (2H, m), 8.02-7.88 (3H, m), 7.83-7.73 (1H, m), 7.67-7.57 (1H, m), 6.70-6.58 (2H, m), 4.80-4.68 (1H, m), 4.33 (1H, d, J=17Hz), 4.13 (1H, d, J=12Hz), 3.82 (3H, s), 3.56-3.25 (6H, m), 2.57-2.47 (1H, m), 2.04-1.54 (4H, m)
29	CDCl <sub>3</sub> : 8.39-8.31 (1H, m), 8.31-8.18 (2H, m), 8.00-7.88 (3H, m), 7.86-7.75 (1H, m), 7.65-7.58 (1H, m), 6.64 (2H, d, J=7Hz), 5.22-5.07 (1H, m), 4.80-4.72 (1H, m), 4.36-4.25 (1H, m), 4.07 (1H, d, J=11Hz), 3.57-3.25 (6H, m), 2.46 (1H, d, J=11Hz), 1.88-1.72 (2H, m), 1.72-1.50 (2H, m), 1.39 (3H, d, J=6Hz), 1.34 (3H, d, J=6Hz)
30	CDCl <sub>3</sub> : 8.39-8.32 (1H, m), 8.31-8.18 (2H, m), 8.00-7.88 (3H, m), 7.82-7.74 (1H, m), 7.66-7.57 (1H, m), 6.70-6.55 (2H, m), 4.83-4.70 (1H, m), 4.32 (1H, d, J=17Hz), 4.25-4.05 (3H, m), 3.58-3.23 (6H, m), 2.55-2.44 (1H, m), 2.00-1.50 (6H, m), 1.05-0.93 (3H, m)
31	CDCl <sub>3</sub> : 8.36 (1H, s), 8.32-8.17 (2H, m), 8.04-7.85 (3H, m), 7.83-7.72 (1H, m), 7.68-7.56 (1H, m), 6.70-6.55 (2H, m), 6.05-5.85 (1H, m), 5.48-5.26 (2H, m), 4.85-4.60 (3H, m), 4.33 (1H, d, J=17Hz), 4.12 (1H, d, J=12Hz), 3.57-3.20 (6H, m), 2.51 (1H, d, J=12Hz), 1.90-1.72 (2H, m), 1.72-1.50 (2H, m)

FIG. 25

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
32	CDCl <sub>3</sub> *: 8.36 (1H, s), 8.31-8.18 (2H, m), 8.03-7.87 (3H, m), 7.83-7.73 (1H, m), 7.67-7.56 (1H, m), 6.72-6.56 (2H, m), 4.78 (1H, d, J=12Hz), 4.45-4.25 (3H, m), 4.10 (1H, d, J=12Hz), 3.75-3.58 (2H, m), 3.40 (3H, m), 3.57-3.23 (6H, m), 2.51 (1H, d, J=12Hz), 1.93-1.53 (4H, m)
33	CDCl <sub>3</sub> *: 8.38-8.32 (1H, m), 8.32-8.20 (2H, m), 8.01-7.91 (3H, m), 7.82-7.75 (1H, m), 7.66-7.58 (1H, m), 6.68-6.60 (2H, m), 4.79-4.70 (1H, m), 4.32 (1H, d, J=17Hz), 4.04 (1H, d, J=12Hz), 3.56-3.22 (5H, m), 3.28 (1H, d, J=17Hz), 2.42 (1H, d, J=2, 11Hz), 1.92-1.76 (2H, m), 1.70-1.48 (2H, m), 1.58 (9H, s)
34	CDCl <sub>3</sub> *: 8.38-8.31 (1H, m), 8.31-8.16 (2H, m), 8.00-7.90 (3H, m), 7.82-7.73 (1H, m), 7.65-7.58 (1H, m), 6.92-6.82 (1H, m), 6.70-6.60 (2H, m), 4.80-4.71 (1H, m), 4.39-4.18 (3H, m), 4.14-4.00 (1H, m), 3.64-3.20 (6H, m), 2.54-2.43 (1H, m), 2.40-1.55 (7H, m), 1.40-1.29 (3H, m)
35(+)	CDCl <sub>3</sub> *: 8.38-8.34 (1H, m), 8.30-8.22 (2H, m), 7.99-7.92 (3H, m), 7.78 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 6.66-6.60 (2H, m), 4.81-4.73 (1H, m), 4.38-4.24 (3H, m), 4.11 (1H, d, J=12Hz), 3.54-3.24 (6H, m), 2.49 (1H, d, J=12Hz), 1.84-1.77 (2H, m), 1.67-1.58 (2H, m), 1.36 (3H, t, J=7Hz)
35(-)	CDCl <sub>3</sub> *: 8.38-8.34 (1H, m), 8.29-8.23 (2H, m), 7.99-7.92 (3H, m), 7.78 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 6.66-6.60 (2H, m), 4.81-4.73 (1H, m), 4.38-4.24 (3H, m), 4.11 (1H, d, J=12Hz), 3.54-3.25 (6H, m), 2.49 (1H, d, J=12Hz), 1.84-1.76 (2H, m), 1.68-1.58 (2H, m), 1.36 (3H, t, J=7Hz)
36	DMSO-d <sub>6</sub> *: 13.24 (1H, s), 8.64 (1H, s), 8.35-8.20 (5H, m), 7.95-7.85 (1H, m), 7.76 (1H, dd, J=2, 9Hz), 7.35-7.20 (2H, m), 4.50-4.35 (1H, m), 4.25-4.15 (2H, m), 4.14-4.00 (2H, m), 3.90-3.75 (2H, m), 3.65-3.20 (4H, m), 3.00-2.85 (1H, m), 2.29 (3H, s), 1.90-1.60 (4H, m), 1.25 (3H, t, J=7Hz)
37	DMSO-d <sub>6</sub> *: 8.61 (1H, s), 8.30 (1H, d, J=9Hz), 8.27-8.22 (1H, m), 8.22-8.08 (3H, m), 7.93-7.86 (1H, m), 7.77-7.69 (1H, m), 6.98 (2H, d, J=7Hz), 4.54-4.41 (1H, m), 4.00-3.80 (2H, m), 3.80-3.16 (4H, m), 3.39 (1H, d, J=16Hz), 3.23 (1H, d, J=12Hz), 2.75-2.65 (1H, m), 1.80-1.65 (2H, m), 1.65-1.45 (2H, m)

FIG. 26

Ex. No.	NMR (270MHz) (ppm) (* : 300MHz)
38	CDCl <sub>3</sub> : 8.39-8.33 (1H, m), 8.30-8.22 (2H, m), 8.00-7.91 (3H, m), 7.81-7.74 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.67-6.59 (2H, m), 4.80-4.70 (1H, m), 4.33 (1H, d, J=17Hz), 4.13 (1H, d, J=11Hz), 3.82 (3H, s), 3.54-3.24 (6H, m), 2.56-2.47 (1H, m), 1.90-1.55 (4H, m)
39	CDCl <sub>3</sub> : 8.36-8.33 (1H, m), 8.30-8.21 (2H, m), 8.00-7.90 (3H, m), 7.82-7.70 (1H, m), 7.65-7.58 (1H, m), 6.68-6.58 (2H, m), 5.22-5.08 (1H, m), 4.82-4.71 (1H, m), 4.32 (1H, d, J=17Hz), 4.07 (1H, d, J=12Hz), 3.58-3.23 (5H, m), 3.39 (1H, d, J=12Hz), 2.46 (1H, d, J=11Hz), 1.88-1.72 (2H, m), 1.72-1.53 (2H, m), 1.39 (3H, d, J=6Hz), 1.34 (3H, d, J=6Hz)
40	CDCl <sub>3</sub> : 8.39-8.32 (1H, m), 8.30-8.20 (2H, m), 8.02-7.88 (3H, m), 7.83-7.73 (1H, m), 7.66-7.57 (1H, m), 6.69-6.57 (2H, m), 4.82-4.73 (1H, m), 4.32 (1H, d, J=17Hz), 4.24-4.05 (3H, m), 3.58-3.23 (6H, m), 2.55-2.44 (1H, m), 1.87-1.54 (6H, m), 1.06-0.94 (3H, m)
41	CDCl <sub>3</sub> : 8.33-8.39 (1H, m), 8.30-8.20 (2H, m), 7.99-7.91 (3H, m), 7.82-7.73 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.67-6.58 (2H, m), 6.04-5.88 (1H, m), 5.46-5.30 (2H, m), 4.83-4.63 (3H, m), 4.33 (1H, d, J=17Hz), 4.12 (1H, d, J=12Hz), 3.55-3.22 (6H, m), 2.51 (1H, d, J=12Hz), 1.85-1.75 (2H, m), 1.70-1.57 (2H, m)
42	CDCl <sub>3</sub> : 8.38-8.33 (1H, m), 8.30-8.20 (2H, m), 8.00-7.90 (3H, m), 7.83-7.74 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.67-6.58 (2H, m), 4.83-4.73 (1H, m), 4.42-4.27 (3H, m), 4.09 (1H, d, J=12Hz), 3.75-3.58 (2H, m), 3.40 (3H, s), 3.55-3.22 (6H, m), 2.55-2.46 (1H, m), 1.92-1.53 (4H, m)
43	CDCl <sub>3</sub> : 8.40-8.32 (1H, m), 8.32-8.19 (2H, m), 8.02-7.89 (3H, m), 7.84-7.75 (1H, m), 7.68-7.57 (1H, m), 6.70-6.59 (2H, m), 4.81-4.69 (1H, m), 4.31 (1H, d, J=17Hz), 4.04 (1H, d, J=12Hz), 3.57-3.20 (5H, m), 3.28 (1H, d, J=17Hz), 2.48-2.37 (1H, m), 1.92-1.72 (2H, m), 1.72-1.45 (2H, m), 1.58 (9H, m)
44	CDCl <sub>3</sub> : 14.36 (1H, brs), 8.38-8.34 (1H, m), 8.25-8.17 (2H, m), 8.00-7.93 (3H, m), 7.77 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 7.00-6.91 (2H, m), 4.74 (1H, d, J=12Hz), 4.32 (1H, d, J=17Hz), 4.15 (1H, d, J=12Hz), 3.95-3.80 (2H, m), 3.83 (3H, s), 3.63-3.35 (4H, m), 2.83 (3H, s), 2.57 (1H, d, J=12Hz), 1.95-1.78 (2H, m), 1.76-1.66 (2H, m)

FIG. 27

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
49	CDCl <sub>3</sub> : 14.22 (1H, brs), 8.38-8.32 (1H, m), 8.27-8.17 (2H, m), 8.00-7.90 (3H, m), 7.82-7.74 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.99-6.89 (2H, m), 4.78-4.69 (1H, m), 4.36-4.25 (1H, m), 4.06 (1H, d, J=12Hz) 3.96-3.80 (2H, m), 3.66-3.38 (3H, m), 3.34-3.23 (1H, m), 2.83 (3H, s), 2.51-2.42 (1H, m), 1.99-1.78 (2H, m), 1.75-1.65 (2H, m), 1.58 (9H, s)
50	CD <sub>3</sub> OD*: 8.47 (1H, s), 8.12 (1H, d, J=9Hz), 8.12-7.99 (4H, m), 7.92-7.83 (1H, m), 7.63 (1H, dd, J=2, 9Hz), 6.82-6.74 (2H, m), 4.65-4.55 (1H, m), 4.14 (1H, d, J=16Hz), 3.89 (1H, d, J=12Hz), 3.68-3.25 (6H, m), 2.72-2.64 (1H, m), 2.02-1.87 (1H, m), 1.82-1.68 (1H, m), 1.68-1.52 (2H, m)
51(+)	CD <sub>3</sub> OD*: 8.49 (1H, s), 8.23-8.01 (5H, m), 7.88-7.86 (1H, m), 7.70-7.61 (1H, m), 6.89-6.71 (2H, m), 4.65-4.54 (1H, m), 4.20-4.08 (1H, m), 3.89 (1H, d, J=12Hz), 3.69-3.18 (6H, m), 2.78-2.64 (1H, m), 2.00-1.52 (4H, m)
51(-)	CD <sub>3</sub> OD*: 8.48 (1H, s), 8.12 (1H, d, J=9Hz), 8.16-8.00 (4H, m), 7.94-7.83 (1H, m), 7.67-7.60 (1H, m), 6.86-6.75 (2H, m), 4.63-4.53 (1H, m), 4.12 (1H, d, J=17Hz), 3.89 (1H, d, J=11Hz), 3.69-3.21 (6H, m), 2.74-2.65 (1H, m), 1.97-1.86 (1H, m), 1.81-1.52 (3H, m)
52	CDCl <sub>3</sub> : 8.33 (1H, s), 8.24-8.13 (2H, m), 7.99-7.89 (3H, m), 7.80-7.69 (3H, m), 7.59 (1H, dd, J=2, 9Hz), 7.22-7.13 (2H, m), 7.12-7.06 (2H, m), 4.79-4.68 (1H, m), 4.36-4.21 (3H, m), 4.19-4.02 (3H, m), 3.98-3.84 (2H, m), 3.56-3.28 (4H, m), 2.59-2.50 (1H, m), 2.30 (3H, s), 1.87-1.72 (2H, m), 1.70-1.55 (2H, m), 1.46-1.30 (6H, m)
53	CD <sub>3</sub> OD: 8.52-8.48 (1H, m), 8.16-8.04 (3H, m), 7.88 (1H, dd, J=2, 9Hz), 7.69-7.60 (3H, m), 7.04-6.95 (2H, m), 4.35-4.10 (3H, m), 3.39 (3H, s), 3.68-3.22 (8H, m), 2.58 (1H, d, J=12Hz), 1.98-1.86 (2H, m), 1.62-1.51 (2H, m)
54	CDCl <sub>3</sub> : 8.54-8.49 (2H, m), 8.36-8.33 (1H, m), 7.97-7.91 (3H, m), 7.80-7.75 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 7.24-7.19 (2H, m), 4.40-4.30 (2H, m), 4.19 (1H, d, J=12Hz), 3.46 (2H, s), 3.41 (3H, s), 3.68-3.52 (2H, m), 3.32 (1H, d, J=17Hz), 3.12 (1H, d, J=12Hz), 2.66-2.54 (1H, m), 2.52-2.20 (3H, m), 2.25 (1H, d, J=12Hz), 2.00-1.77 (2H, m), 1.54-1.36 (2H, m)



FIG. 28

Ex.No.	NMR (* : 300MHz) (270MHz) (ppm)
55	CDCl <sub>3</sub> *: 8.38-8.34 (1H, m), 8.20-7.92 (5H, m), 7.78 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 6.65-6.58 (2H, m), 4.42-4.30 (2H, m), 4.21 (1H, d, J=12Hz), 3.67 (1H, d, J=10Hz), 3.63 (1H, d, J=10Hz), 3.43 (3H, s), 3.50-3.18 (6H, m), 2.30 (1H, d, J=12Hz), 2.06-1.80 (2H, m), 1.59-1.50 (2H, m)
56	CDCl <sub>3</sub> *: 8.37-8.33 (1H, m), 7.98-7.91 (3H, m), 7.81-7.75 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 4.40-4.30 (2H, m), 4.19 (1H, d, J=12Hz), 3.69-3.56 (2H, m), 3.42 (3H, s), 3.54-3.26 (4H, m), 3.34 (1H, d, J=17Hz), 3.18 (1H, d, J=12Hz), 2.28 (1H, d, J=12Hz), 2.06 (3H, s), 1.94-1.72 (2H, m), 1.46-1.38 (2H, m)
57	DMSO-d <sub>6</sub> (100°C) *: 9.04-8.70 (1H, m), 8.56-8.51 (1H, m), 8.50-8.30 (1H, m), 8.23 (1H, d, J=9Hz), 8.19-8.10 (2H, m), 7.86 (1H, dd, J=2, 9Hz), 7.71-7.65 (1H, m), 4.16-4.03 (3H, m), 3.79-2.44 (9H, m), 3.28 (3H, s), 2.32 (3H, s), 2.28-2.21 (3H, m), 1.99-1.84 (2H, m), 1.68-1.58 (2H, m)
58	CDCl <sub>3</sub> *: 8.39-8.33 (1H, m), 8.28-8.20 (2H, m), 7.99-7.90 (3H, m), 7.84-7.76 (1H, m), 7.65-7.58 (1H, m), 6.66-6.58 (2H, m), 4.53 (1H, d, J=12Hz), 4.38 (1H, d, J=17Hz), 4.26 (1H, d, J=12Hz), 3.55-3.10 (7H, m), 2.89 (1H, d, J=14Hz), 2.24 (1H, d, J=12Hz), 1.94-1.84 (2H, m), 1.57-1.48 (2H, m)
59	DMSO-d <sub>6</sub> *: 8.56-8.52 (1H, m), 8.22 (1H, d, J=9Hz), 8.18-8.08 (4H, m), 7.91-7.85 (1H, m), 7.70-7.64 (1H, m), 6.74-6.64 (3H, m), 4.14-3.96 (5H, m), 3.62 (1H, d, J=16Hz), 3.50-3.12 (6H, m), 3.08 (1H, d, J=12Hz), 2.81 (1H, d, J=12Hz), 1.90-1.74 (2H, m), 1.50-1.43 (2H, m), 1.19-1.13 (3H, m)
60	CDCl <sub>3</sub> *: 8.40-8.33 (1H, m), 8.28-8.20 (2H, m), 8.02-7.88 (3H, m), 7.84-7.77 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 6.66-6.58 (2H, m), 4.67 (1H, d, J=11Hz), 4.37 (1H, d, J=17Hz), 4.28-4.15 (3H, m), 3.61-3.21 (7H, m), 3.17 (1H, d, J=12Hz), 2.97 (2H, s), 2.27-1.84 (3H, m), 1.56-1.46 (2H, m), 1.30 (3H, t, J=7Hz)
61	CDCl <sub>3</sub> *: 8.37 (1H, s), 8.28-8.12 (2H, m), 8.02-7.93 (3H, m), 7.85-7.77 (1H, m), 7.66-7.60 (1H, m), 6.66-6.58 (2H, m), 4.72 (1H, d, J=11Hz), 4.36 (1H, d, J=17Hz), 4.27 (1H, d, J=12Hz), 3.77-3.67 (4H, m), 3.56-3.17 (6H, m), 2.94-2.46 (6H, m), 2.15 (1H, d, J=11Hz), 2.00-1.70 (2H, m), 1.54-1.43 (2H, m)

FIG. 29

Ex. No.	NMR (270MHz) (ppm) (* : 300MHz)
62	DMSO-d <sub>6</sub> : 13.3 (1H, brs), 8.62 (1H, s), 8.33 (1H, d, J=9Hz), 8.31-8.16 (4H, m), 7.95-7.87 (1H, m), 7.80-7.72 (1H, m), 7.19 (2H, d, J=7Hz), 4.51-4.40 (1H, m), 4.34-4.05 (2H, m), 4.05-2.20 (17H, m), 2.34 (6H, s), 2.04-1.82 (2H, m), 1.66-1.46 (2H, m)
63	CDCl <sub>3</sub> : 8.40-8.35 (1H, m), 8.05-8.00 (1H, m), 8.00-7.93 (3H, m), 7.84-7.77 (1H, m), 7.63 (1H, dd, J=9, 2Hz), 6.49-6.35 (1H, m), 4.55-4.48 (1H, m), 4.42 (1H, d, J=12Hz), 4.42-4.33 (1H, m), 4.26 (1H, d, J=12Hz), 4.23-4.15 (1H, m), 4.05-3.80 (2H, m), 3.49-3.28 (3H, m), 3.19 (1H, d, J=12Hz), 2.37 (1H, d, J=12Hz), 2.13 (3H, s), 2.00-1.89 (1H, m), 1.85-1.73 (1H, m), 1.53-1.43 (2H, m)
64	CDCl <sub>3</sub> : 8.56 (1H, s), 8.40 (1H, s), 8.20-8.15 (1H, m), 8.08-7.93 (3H, m), 7.81-7.63 (3H, m), 6.50-6.44 (1H, m), 4.55-4.15 (3H, m), 4.38 (1H, d, J=17Hz), 4.26 (1H, d, J=12Hz), 3.96-3.80 (2H, m), 3.54-3.30 (2H, m), 3.38 (1H, d, J=17Hz), 3.18 (1H, d, J=12Hz), 2.36 (1H, d, J=12Hz), 2.12 (3H, s), 1.98-1.68 (2H, m), 1.52-1.43 (2H, m)
65	CDCl <sub>3</sub> : 8.56 (1H, s), 8.40-8.36 (1H, m), 8.21-8.15 (1H, m), 8.02-7.94 (3H, m), 7.83-7.77 (1H, m), 7.63 (1H, dd, J=2, 8Hz), 6.50-6.46 (1H, m), 4.51 (1H, d, J=12Hz), 4.47-4.23 (3H, m), 4.19 (1H, d, J=12Hz), 3.96-3.83 (2H, m), 3.53-3.34 (3H, m), 3.18 (1H, d, J=12Hz), 2.38 (1H, d, J=12Hz), 2.13 (3H, s), 1.98-1.88 (1H, m), 1.85-1.59 (1H, m), 1.52-1.45 (2H, m)
66	CDCl <sub>3</sub> : 8.57 (1H, s), 8.39-8.35 (1H, m), 8.28-8.12 (1H, m), 7.99-7.93 (3H, m), 7.82-7.76 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.53-6.46 (1H, m), 4.49-4.24 (3H, m), 3.94 (1H, d, J=12Hz), 3.99-3.76 (2H, m), 3.73 (1H, d, J=12Hz), 3.69-3.55 (1H, m), 3.51-3.36 (2H, m), 3.20 (1H, d, J=12Hz), 2.34 (1H, d, J=12Hz), 1.98-1.60 (2H, m), 1.54-1.46 (2H, m)
67	CDCl <sub>3</sub> : 8.57 (1H, s), 8.38-8.34 (1H, m), 8.22-8.17 (1H, m), 7.98-7.93 (3H, m), 7.82-7.75 (1H, m), 7.65-7.60 (1H, dd, J=2, 8Hz), 6.52-6.46 (1H, m), 4.82-4.74 (1H, m), 4.37-4.24 (3H, m), 4.11 (1H, d, J=12Hz), 3.97-3.85 (2H, m), 3.60-3.32 (4H, m), 2.50 (1H, d, J=12Hz), 1.85-1.54 (4H, m), 1.36 (3H, t, J=7Hz)

FIG. 30

Ex. No.	NMR (270MHz) (ppm) (* : 300MHz)
68	CD <sub>3</sub> OD+CDCl <sub>3</sub> : 8.47-8.40 (2H, m), 8.10-7.99 (4H, m), 7.86 (1H, dd, J=2, 9Hz), 7.67-7.60 (1H, m), 6.70-6.64 (1H, m), 4.67 (1H, d, J=11Hz), 4.20 (1H, d, J=16Hz), 4.08-3.94 (2H, m), 3.90 (1H, d, J=12Hz), 3.68-3.31 (4H, m), 2.63 (1H, d, J=11Hz), 2.02-1.92 (1H, m), 1.78-1.66 (1H, m), 1.65-1.54 (2H, m)
69	CDCl <sub>3</sub> : 8.37-8.34 (1H, m), 8.28-8.22 (2H, m), 7.99-7.92 (3H, m), 7.82-7.75 (1H, m), 7.65-7.59 (1H, m), 6.65-6.59 (2H, m), 4.35 (1H, d, J=17Hz), 4.27-4.12 (2H, m), 3.31 (1H, d, J=17Hz), 3.56-3.17 (4H, m), 3.13 (1H, d, J=12Hz), 2.37 (1H, d, J=11Hz), 1.93-1.83 (2H, m), 1.64 (3H, s), 1.53-1.45 (2H, m)
70	CDCl <sub>3</sub> : 14.49 (1H, brs), 8.36 (1H, s), 8.32-8.12 (2H, m), 8.05-7.89 (3H, m), 7.79 (1H, d, J=8Hz), 7.63 (1H, d, J=9Hz), 7.05-6.75 (2H, m), 4.35 (1H, d, J=17Hz), 4.30-4.10 (2H, m), 4.01-3.70 (2H, m), 3.70-3.52 (1H, m), 3.52-3.33 (1H, m), 3.33 (1H, d, J=17Hz), 3.25-3.12 (1H, m), 2.85 (3H, s), 2.48-2.35 (1H, m), 2.02-1.80 (2H, m), 1.72-1.49 (2H, m), 1.66 (3H, s)
71	CDCl <sub>3</sub> : 8.39-8.33 (1H, m), 8.29-8.21 (2H, m), 8.00-7.90 (3H, m), 7.83-7.76 (1H, m), 7.65-7.58 (1H, m), 6.66-6.59 (2H, m), 4.40-4.26 (2H, m), 4.20 (1H, d, J=12Hz), 3.71 (3H, s), 3.59-3.48 (1H, m), 3.48-3.33 (2H, m), 3.34 (1H, d, J=17Hz), 3.33-3.18 (1H, m), 3.13 (1H, d, J=12Hz), 2.50-2.31 (2H, m), 2.27 (1H, d, J=12Hz), 2.14-1.70 (6H, m), 1.56-1.45 (2H, m)
72	DMSO-d <sub>6</sub> : 8.58 (1H, s), 8.32-7.96 (5H, m), 7.96-7.78 (1H, m), 7.74-7.60 (1H, m), 6.84-6.62 (2H, m), 4.19-3.95 (3H, m), 3.72-2.94 (6H, m), 2.63-1.00 (12H, m)
73	CDCl <sub>3</sub> : 8.36-8.33 (1H, m), 8.26-8.21 (2H, m), 7.98-7.92 (3H, m), 7.80-7.75 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.64-6.59 (2H, m), 4.36 (1H, d, J=17Hz), 4.27-4.17 (2H, m), 4.06-4.00 (1H, m), 3.65-3.58 (1H, m), 3.53-3.16 (5H, m), 3.02 (1H, d, J=12Hz), 2.46 (1H, brs), 2.29 (1H, d, J=12Hz), 1.93-1.75 (2H, m), 1.49-1.41 (2H, m)
74	CDCl <sub>3</sub> : 8.35 (1H, s), 8.28-8.18 (2H, m), 8.01-7.88 (3H, m), 7.82-7.72 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.68-6.58 (2H, m), 4.35 (1H, d, J=12Hz), 4.34 (1H, d, J=17Hz), 4.25-4.18 (1H, m), 4.00-3.68 (4H, m), 3.43 (1H, d, J=17Hz), 3.20-3.12 (1H, m), 3.03-2.70 (2H, m), 2.42 (1H, d, J=12Hz), 2.42 (3H, s), 2.10-1.95 (1H, m), 1.84-1.66 (2H, m), 1.15-1.02 (1H, m)

FIG. 31

Ex. No.	NMR (270MHz) (* : 300MHz) (ppm)
75	CDCl <sub>3</sub> *: 8.38-8.33 (1H, m), 8.28-8.22 (2H, m), 8.00-7.90 (3H, m), 7.82-7.74 (1H, m), 7.65-7.58 (1H, m), 6.65-6.55 (2H, m), 4.38-4.15 (3H, m), 3.97-3.87 (1H, m), 3.83-3.72 (1H, m), 3.75 (1H, d, J=10Hz), 3.67 (1H, d, J=10Hz), 3.38 (3H, s), 3.34 (1H, d, J=17Hz), 3.22 (1H, d, J=11Hz), 2.87-2.66 (2H, m), 2.37 (3H, s), 2.26 (1H, d, J=11Hz), 1.98-1.81 (2H, m), 1.77-1.58 (1H, m), 1.15-1.05 (1H, m)
76	CD <sub>3</sub> OD*: 8.56-8.52 (1H, m), 8.18-8.06 (5H, m), 7.91 (1H, dd, J=2, 9Hz), 7.66 (1H, dd, J=2, 9Hz), 7.18-7.12 (2H, m), 4.51 (1H, d, J=12Hz), 4.43-4.28 (3H, m), 4.26-4.15 (1H, m), 3.89-3.75 (2H, m), 3.50 (1H, d, J=16Hz), 3.39 (3H, s), 3.56-3.11 (3H, m), 2.77-2.66 (1H, m), 2.68 (6H, s), 2.61 (3H, s), 2.15-2.02 (2H, m), 1.93-1.77 (1H, m), 1.50-1.40 (1H, m)
77	CDCl <sub>3</sub> *: 8.38-8.32 (1H, m), 8.28-8.20 (2H, m), 8.00-7.90 (3H, m), 7.82-7.75 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 6.63-6.56 (2H, m), 4.35 (1H, d, J=17Hz), 4.23-4.12 (2H, m), 3.73 (1H, d, J=10Hz), 3.48 (1H, d, J=10Hz), 3.53-3.13 (5H, m), 3.44 (3H, s), 2.97 (1H, d, J=12Hz), 2.52-2.44 (1H, brs), 2.24 (1H, d, J=12Hz), 1.91-1.69 (2H, m), 1.47-1.30 (2H, m)
78	CDCl <sub>3</sub> *: 8.37-8.32 (1H, m), 8.31-8.24 (2H, m), 8.00-7.90 (3H, m), 7.81-7.74 (1H, m), 7.61 (1H, d, J=2, 9Hz), 6.67-6.60 (2H, m), 5.15 (1H, d, J=13Hz), 4.67 (1H, d, J=11Hz), 4.45 (1H, d, J=17Hz), 4.34 (1H, d, J=10Hz), 4.00-3.77 (2H, m), 3.89 (1H, d, J=10Hz), 3.51-3.28 (2H, m), 3.36 (3H, s), 3.05-2.90 (1H, m), 2.85-2.71 (1H, m), 2.55-2.38 (1H, m), 2.32 (1H, d, J=13Hz), 2.20-1.95 (2H, m), 2.10 (3H, s), 1.41-1.22 (1H, m)
79	CDCl <sub>3</sub> *: 8.40-8.35 (1H, m), 8.28-8.20 (2H, m), 8.07-7.93 (3H, m), 7.81-7.63 (3H, m), 6.65-6.57 (2H, m), 4.36 (1H, d, J=17Hz), 4.24-4.14 (2H, m), 3.74 (1H, d, J=9Hz), 3.53-3.13 (6H, m), 3.45 (3H, s), 2.97 (1H, d, J=12Hz), 2.51-2.44 (1H, brs), 2.24 (1H, d, J=12Hz), 1.92-1.68 (2H, m), 1.47-1.28 (2H, m)
80	CDCl <sub>3</sub> *: 8.40-8.34 (1H, m), 8.28-8.21 (2H, m), 8.07-7.92 (3H, m), 7.79-7.62 (3H, m), 6.66-6.57 (2H, m), 4.34 (1H, d, J=17Hz), 4.28-4.14 (2H, m), 3.97-3.87 (1H, m), 3.83-3.65 (3H, m), 3.38 (3H, s), 3.35 (1H, d, J=17Hz), 3.21 (1H, d, J=11Hz), 2.88-2.67 (2H, m), 2.37 (3H, s), 2.24 (1H, d, J=12Hz), 1.98-1.80 (2H, m), 1.77-1.62 (1H, m), 1.15-1.05 (1H, m)

FIG. 32

Ex. No.	NMR (270MHz) (ppm) (* : 300MHz)
81	CDCl <sub>3</sub> : 8.40-8.36 (1H, m), 8.28-8.20 (2H, m), 8.07-7.92 (3H, m), 7.81-7.60 (3H, m), 6.64-6.58 (2H, m), 4.43-4.32 (2H, m), 4.20 (1H, d, J=12Hz), 3.72-3.60 (2H, m), 3.50-3.17 (5H, m), 3.44 (3H, s), 3.35 (1H, d, J=17Hz), 2.28 (1H, d, J=12Hz), 2.03-1.78 (2H, m), 1.54-1.46 (2H, m)
82	CDCl <sub>3</sub> : 8.40-8.36 (1H, m), 8.28-8.20 (2H, m), 8.06-7.92 (3H, m), 7.79-7.64 (3H, m), 6.64-6.57 (2H, m), 4.43-4.30 (2H, m), 4.20 (1H, d, J=12Hz), 3.68 (1H, d, J=10Hz), 3.63 (1H, d, J=10Hz), 3.49-3.17 (5H, m), 3.44 (3H, s), 3.35 (1H, d, J=17Hz), 2.28 (1H, d, J=12Hz), 2.03-1.79 (2H, m), 1.53-1.45 (2H, m)

FIG. 33

&lt;TABLE A&gt;

COORDINATES OF THE ACTIVE CENTER SITES IN THE CRYSTAL  
STRUCTURE OF COMPOUND A - FXA COMPLEX ARE SHOWN  
BELOW IN PDB FORMAT

①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩
ATOM	784	N	LYS	96	4.741	10.202	10.448	1.00	23.85
ATOM	785	H	LYS	96	5.064	9.293	10.312	1.00	0.00
ATOM	786	CA	LYS	96	4.804	11.268	9.454	1.00	22.65
ATOM	787	CB	LYS	96	5.745	10.872	8.307	1.00	27.27
ATOM	788	CG	LYS	96	6.091	9.385	8.228	1.00	30.35
ATOM	789	CD	LYS	96	7.164	9.009	9.239	1.00	29.56
ATOM	790	CE	LYS	96	7.405	7.504	9.282	1.00	32.56
ATOM	791	NZ	LYS	96	6.242	6.736	9.818	1.00	28.13
ATOM	792	HZ1	LYS	96	5.404	6.920	9.230	1.00	0.00
ATOM	793	HZ2	LYS	96	6.041	7.047	10.791	1.00	0.00
ATOM	794	HZ3	LYS	96	6.459	5.720	9.815	1.00	0.00
ATOM	795	C	LYS	96	3.431	11.693	8.910	1.00	20.65
ATOM	796	O	LYS	96	3.285	12.797	8.388	1.00	16.33
ATOM	797	N	GLU	97	2.422	10.839	9.093	1.00	19.10
ATOM	798	H	GLU	97	2.641	10.040	9.589	1.00	0.00
ATOM	799	CA	GLU	97	1.066	11.119	8.610	1.00	19.57
ATOM	800	CB	GLU	97	0.233	9.842	8.507	1.00	18.38
ATOM	801	CG	GLU	97	0.703	8.698	9.374	1.00	29.43
ATOM	802	CD	GLU	97	1.871	7.943	8.757	1.00	39.21
ATOM	803	OE1	GLU	97	2.967	7.943	9.362	1.00	48.48
ATOM	804	OE2	GLU	97	1.693	7.350	7.666	1.00	41.77
ATOM	805	C	GLU	97	0.309	12.140	9.438	1.00	19.94
ATOM	806	O	GLU	97	-0.542	12.860	8.929	1.00	15.85
ATOM	807	N	THR	98	0.604	12.181	10.728	1.00	21.36
ATOM	808	H	THR	98	1.261	11.557	11.087	1.00	0.00
ATOM	809	CA	THR	98	-0.056	13.124	11.626	1.00	21.20
ATOM	810	CB	THR	98	-0.611	12.419	12.855	1.00	20.12
ATOM	811	OG1	THR	98	0.473	11.796	13.553	1.00	25.14
ATOM	812	HG1	THR	98	0.192	11.011	14.047	1.00	0.00
ATOM	813	CG2	THR	98	-1.640	11.363	12.458	1.00	26.75
ATOM	814	C	THR	98	0.947	14.110	12.156	1.00	19.21
ATOM	815	O	THR	98	0.591	15.212	12.538	1.00	22.96
ATOM	816	N	TYR	99	2.209	13.691	12.171	1.00	18.62
ATOM	817	H	TYR	99	2.395	12.809	11.804	1.00	0.00
ATOM	818	CA	TYR	99	3.304	14.486	12.711	1.00	17.73
ATOM	819	CB	TYR	99	3.410	15.846	12.010	1.00	14.99
ATOM	820	CG	TYR	99	4.440	15.851	10.912	1.00	14.90
ATOM	821	CD1	TYR	99	5.423	16.839	10.848	1.00	15.28
ATOM	822	CE1	TYR	99	6.420	16.804	9.870	1.00	17.93
ATOM	823	CD2	TYR	99	4.477	14.828	9.968	1.00	18.54
ATOM	824	CE2	TYR	99	5.464	14.786	8.993	1.00	25.43
ATOM	825	CZ	TYR	99	6.432	15.771	8.954	1.00	25.32
ATOM	826	OH	TYR	99	7.412	15.709	7.995	1.00	32.89
ATOM	827	HH	TYR	99	7.202	15.004	7.373	1.00	0.00
ATOM	828	C	TYR	99	3.098	14.642	14.220	1.00	18.17
ATOM	829	O	TYR	99	3.565	15.592	14.844	1.00	21.63
ATOM	1577	N	PHE	174	-4.467	21.058	8.884	1.00	13.87
ATOM	1578	H	PHE	174	-4.036	21.860	9.243	1.00	0.00
ATOM	1579	CA	PHE	174	-4.243	19.756	9.527	1.00	14.33
ATOM	1580	CB	PHE	174	-2.773	19.378	9.454	1.00	8.22
ATOM	1581	CG	PHE	174	-2.290	19.047	8.090	1.00	4.53
ATOM	1582	CD1	PHE	174	-2.151	17.728	7.701	1.00	2.00
ATOM	1583	CD2	PHE	174	-1.861	20.046	7.229	1.00	8.32
ATOM	1584	CE1	PHE	174	-1.582	17.407	6.477	1.00	4.74
ATOM	1585	CE2	PHE	174	-1.288	19.729	6.002	1.00	8.59
ATOM	1586	CZ	PHE	174	-1.148	18.407	5.632	1.00	11.56

FIG. 34

CONTINUED FROM &lt;TABLE A&gt;

ATOM	1587	C	PHE	174	-4.654	19.705	11.000	1.00	16.38
ATOM	1588	O	PHE	174	-4.788	20.738	11.654	1.00	20.64
ATOM	1745	N	ASP	189	8.408	33.948	10.783	1.00	12.09
ATOM	1746	H	ASP	189	9.304	34.162	10.443	1.00	0.00
ATOM	1747	CA	ASP	189	8.045	32.569	11.126	1.00	14.13
ATOM	1748	CB	ASP	189	7.060	32.074	10.052	1.00	18.27
ATOM	1749	CG	ASP	189	8.299	30.818	10.447	1.00	29.21
ATOM	1750	OD1	ASP	189	6.899	29.872	11.005	1.00	26.93
ATOM	1751	OD2	ASP	189	5.077	30.767	10.152	1.00	28.08
ATOM	1752	C	ASP	189	9.333	31.731	11.053	1.00	14.52
ATOM	1753	O	ASP	189	10.370	32.219	10.606	1.00	17.15
ATOM	1754	N	ALA	190	9.301	30.508	11.571	1.00	10.01
ATOM	1755	H	ALA	190	8.522	30.238	12.091	1.00	0.00
ATOM	1756	CA	ALA	190	10.453	29.620	11.470	1.00	5.72
ATOM	1757	CB	ALA	190	10.325	28.473	12.450	1.00	9.56
ATOM	1758	C	ALA	190	10.396	29.112	10.025	1.00	5.82
ATOM	1759	O	ALA	190	9.799	29.761	9.186	1.00	9.42
ATOM	1760	N	CYS	191	10.988	27.960	9.728	1.00	3.41
ATOM	1761	H	CYS	191	11.414	27.439	10.437	1.00	0.00
ATOM	1762	CA	CYS	191	10.979	27.440	8.360	1.00	6.67
ATOM	1763	C	CYS	191	11.864	26.196	8.255	1.00	5.52
ATOM	1764	O	CYS	191	12.375	25.715	9.277	1.00	6.15
ATOM	1765	CB	CYS	191	11.469	28.518	7.387	1.00	8.63
ATOM	1766	SG	CYS	191	11.102	28.223	5.629	1.00	18.50
ATOM	1767	N	GLN	192	12.098	25.713	7.033	1.00	5.87
ATOM	1768	H	GLN	192	11.679	26.167	6.270	1.00	0.00
ATOM	1769	CA	GLN	192	12.925	24.515	6.820	1.00	10.96
ATOM	1770	CB	GLN	192	13.086	24.254	5.331	1.00	17.72
ATOM	1771	CG	GLN	192	13.700	22.910	5.018	1.00	32.49
ATOM	1772	CD	GLN	192	14.143	22.802	3.575	1.00	41.58
ATOM	1773	OET	GLN	192	15.327	22.950	3.264	1.00	44.38
ATOM	1774	NE2	GLN	192	13.194	22.551	2.678	1.00	43.85
ATOM	1775	HE21	GLN	192	12.259	22.433	2.903	1.00	0.00
ATOM	1776	HE22	GLN	192	13.527	22.509	1.763	1.00	0.00
ATOM	1777	C	GLN	192	14.316	24.525	7.478	1.00	7.56
ATOM	1778	O	GLN	192	14.974	25.563	7.548	1.00	2.44
ATOM	1779	N	GLY	193	14.761	23.372	7.964	1.00	8.11
ATOM	1780	H	GLY	193	14.237	22.555	7.869	1.00	0.00
ATOM	1781	CA	GLY	193	16.064	23.313	8.603	1.00	9.56
ATOM	1782	C	GLY	193	16.035	23.720	10.065	1.00	11.52
ATOM	1783	O	GLY	193	16.889	23.315	10.843	1.00	15.90
ATOM	1784	N	ASP	194	15.080	24.571	10.431	1.00	12.53
ATOM	1785	H	ASP	194	14.493	24.947	9.749	1.00	0.00
ATOM	1786	CA	ASP	194	14.915	24.987	11.814	1.00	7.55
ATOM	1787	CB	ASP	194	13.908	26.131	11.915	1.00	2.00
ATOM	1788	CG	ASP	194	14.475	27.465	11.459	1.00	2.00
ATOM	1789	OD1	ASP	194	13.728	28.235	10.814	1.00	4.12
ATOM	1790	OD2	ASP	194	15.651	27.765	11.761	1.00	7.76
ATOM	1791	C	ASP	194	14.402	23.791	12.621	1.00	9.73
ATOM	1792	O	ASP	194	14.536	23.750	13.840	1.00	12.71
ATOM	1793	N	SER	195	13.804	22.823	11.938	1.00	6.99
ATOM	1794	H	SER	195	13.748	22.953	10.974	1.00	0.00
ATOM	1795	CA	SER	195	13.264	21.625	12.589	1.00	10.57
ATOM	1796	CB	SER	195	12.968	20.532	11.555	1.00	10.36
ATOM	1797	OG	SER	195	11.748	20.787	10.868	1.00	8.45
ATOM	1798	HG	SER	195	11.756	21.696	10.548	1.00	0.00
ATOM	1799	C	SER	195	14.136	21.054	13.707	1.00	8.30
ATOM	1800	O	SER	195	15.298	20.752	13.486	1.00	13.26
ATOM	1965	N	VAL	213	10.619	22.878	17.479	1.00	8.87
ATOM	1966	H	VAL	213	11.529	23.087	17.805	1.00	0.00

FIG. 35

CONTINUED FROM &lt;TABLE A&gt;

ATOM	1967	CA	VAL	213	10.217	23.245	16.105	1.00	3.61
ATOM	1968	CB	VAL	213	11.363	23.956	15.352	1.00	4.20
ATOM	1969	CG1	VAL	213	11.061	24.047	13.872	1.00	2.00
ATOM	1970	CG2	VAL	213	11.554	25.346	15.896	1.00	2.00
ATOM	1971	C	VAL	213	9.808	21.980	15.336	1.00	5.71
ATOM	1972	O	VAL	213	10.634	21.095	15.120	1.00	2.00
ATOM	1973	N	SER	214	8.540	21.914	14.921	1.00	8.94
ATOM	1974	H	SER	214	7.946	22.664	15.112	1.00	0.00
ATOM	1975	CA	SER	214	8.004	20.737	14.221	1.00	8.85
ATOM	1976	CB	SER	214	6.839	20.152	15.020	1.00	10.34
ATOM	1977	CG	SER	214	6.380	18.937	14.453	1.00	8.56
ATOM	1978	HG	SER	214	5.666	18.601	15.008	1.00	0.00
ATOM	1979	C	SER	214	7.592	20.874	12.744	1.00	12.05
ATOM	1980	O	SER	214	8.239	20.305	11.862	1.00	14.40
ATOM	1981	N	TRP	215	6.490	21.567	12.478	1.00	14.50
ATOM	1982	H	TRP	215	5.987	21.982	13.213	1.00	0.00
ATOM	1983	CA	TRP	215	6.011	21.750	11.101	1.00	11.54
ATOM	1984	CB	TRP	215	5.193	20.536	10.632	1.00	11.75
ATOM	1985	CG	TRP	215	3.961	20.290	11.450	1.00	12.42
ATOM	1986	CD2	TRP	215	2.631	20.752	11.174	1.00	18.81
ATOM	1987	CE2	TRP	215	1.811	20.311	12.230	1.00	16.79
ATOM	1988	CE3	TRP	215	2.051	21.492	10.133	1.00	25.81
ATOM	1989	CD1	TRP	215	3.891	19.611	12.617	1.00	12.16
ATOM	1990	NE1	TRP	215	2.607	19.618	13.097	1.00	17.72
ATOM	1991	HE1	TRP	215	2.296	19.183	13.914	1.00	0.00
ATOM	1992	CZ2	TRP	215	0.441	20.585	12.285	1.00	16.94
ATOM	1993	CZ3	TRP	215	0.688	21.767	10.185	1.00	25.39
ATOM	1994	CH2	TRP	215	-0.101	21.310	11.259	1.00	22.37
ATOM	1995	C	TRP	215	5.167	23.007	10.918	1.00	14.86
ATOM	1996	O	TRP	215	4.957	23.789	11.854	1.00	14.41
ATOM	1997	N	GLY	216	4.675	23.173	9.695	1.00	16.84
ATOM	1998	H	GLY	216	4.881	22.520	8.995	1.00	0.00
ATOM	1999	CA	GLY	216	3.850	24.316	9.345	1.00	17.38
ATOM	2000	C	GLY	216	3.471	24.237	7.880	1.00	20.21
ATOM	2001	O	GLY	216	3.922	23.333	7.173	1.00	20.21
ATOM	2002	N	GLU	217	2.587	25.129	7.440	1.00	19.61
ATOM	2003	H	GLU	217	2.216	25.764	8.085	1.00	0.00
ATOM	2004	CA	GLU	217	2.153	25.176	6.042	1.00	12.11
ATOM	2005	CB	GLU	217	0.645	25.351	5.953	1.00	6.63
ATOM	2006	CG	GLU	217	-0.079	24.049	6.207	1.00	20.42
ATOM	2007	CD	GLU	217	-1.531	24.228	6.610	1.00	23.62
ATOM	2008	OE1	GLU	217	-2.230	25.085	6.031	1.00	24.43
ATOM	2009	OE2	GLU	217	-1.975	23.500	7.521	1.00	28.17
ATOM	2010	C	GLU	217	2.897	26.300	5.348	1.00	11.70
ATOM	2011	O	GLU	217	2.504	27.469	5.400	1.00	6.58
ATOM	2012	N	GLY	218	4.013	25.919	4.738	1.00	11.12
ATOM	2013	H	GLY	218	4.256	24.974	4.781	1.00	0.00
ATOM	2014	CA	GLY	218	4.865	26.877	4.065	1.00	15.66
ATOM	2015	C	GLY	218	5.754	27.559	5.090	1.00	12.39
ATOM	2016	O	GLY	218	6.206	26.925	6.034	1.00	15.04
ATOM	2017	N	CYS	220	6.020	28.842	4.900	1.00	9.76
ATOM	2018	H	CYS	220	5.639	29.259	4.101	1.00	0.00
ATOM	2019	CA	CYS	220	6.833	29.599	5.838	1.00	9.17
ATOM	2020	C	CYS	220	6.352	31.034	5.783	1.00	13.52
ATOM	2021	O	CYS	220	6.480	31.710	4.759	1.00	15.23
ATOM	2022	CB	CYS	220	8.336	29.530	5.506	1.00	9.55
ATOM	2023	SG	CYS	220	9.098	27.875	5.612	1.00	10.99
ATOM	2092	N	GLY	226	3.145	28.841	13.069	1.00	12.64
ATOM	2093	H	GLY	226	3.142	29.684	13.567	1.00	0.00
ATOM	2094	CA	GLY	226	4.219	27.901	13.325	1.00	7.11

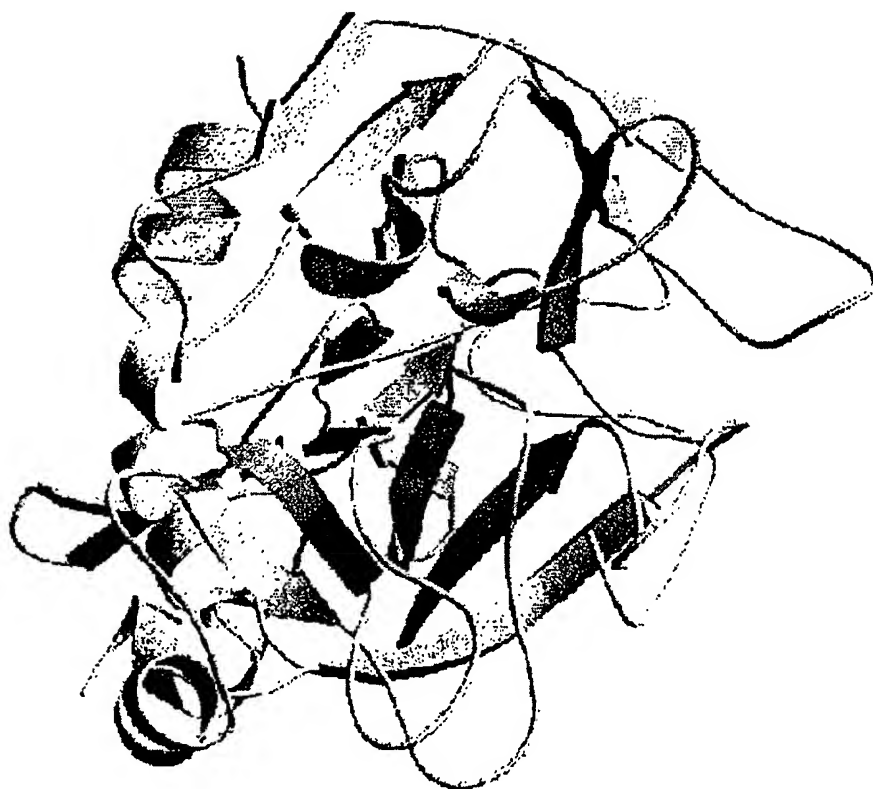


FIG. 36

CONTINUED FROM &lt;TABLE A&gt;

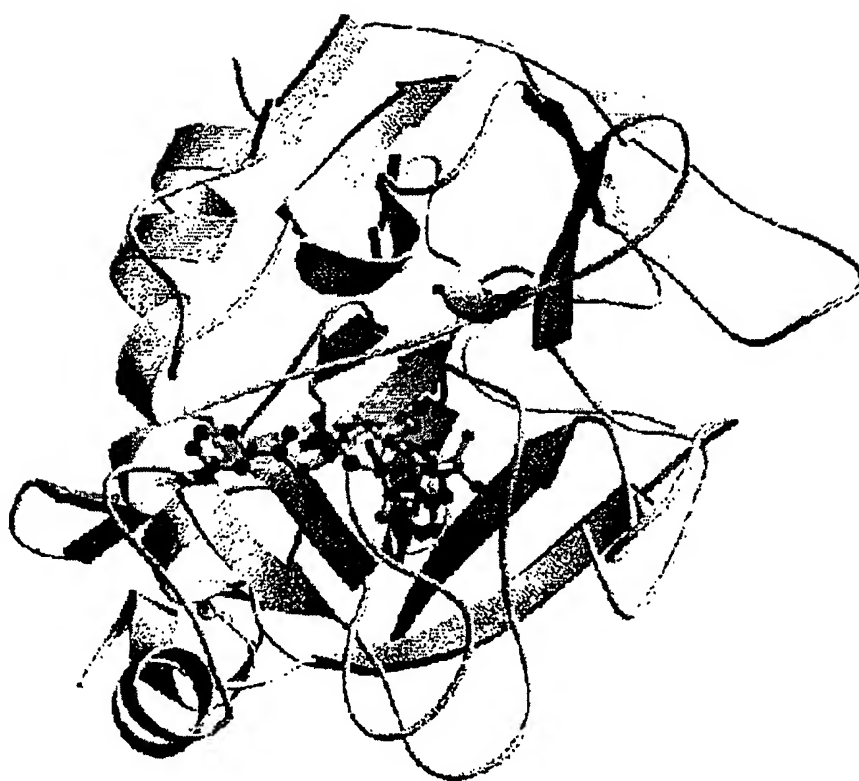
ATOM	2095	C	GLY	226	3.728	26.832	14.287	1.00	2.00
ATOM	2096	O	GLY	226	3.203	27.151	15.355	1.00	2.00
ATOM	2097	N	ILE	227	3.858	25.569	13.899	1.00	2.00
ATOM	2098	H	ILE	227	4.255	25.373	13.019	1.00	0.00
ATOM	2099	CA	ILE	227	3.416	24.465	14.748	1.00	8.14
ATOM	2100	CB	ILE	227	2.711	23.360	13.916	1.00	10.97
ATOM	2101	CG2	ILE	227	2.093	22.318	14.848	1.00	12.70
ATOM	2102	CG1	ILE	227	1.662	23.971	12.978	1.00	10.26
ATOM	2103	CD1	ILE	227	0.580	24.750	13.683	1.00	5.42
ATOM	2104	C	ILE	227	4.593	23.829	15.500	1.00	8.86
ATOM	2105	O	ILE	227	5.455	23.179	14.902	1.00	14.80
ATOM	2106	N	TYR	228	4.632	24.017	16.811	1.00	9.76
ATOM	2107	H	TYR	228	3.915	24.543	17.234	1.00	0.00
ATOM	2108	CA	TYR	228	5.701	23.457	17.628	1.00	5.66
ATOM	2109	CB	TYR	228	6.321	24.544	18.502	1.00	3.07
ATOM	2110	CG	TYR	228	6.709	25.806	17.775	1.00	2.00
ATOM	2111	CD1	TYR	228	5.745	26.627	17.220	1.00	6.58
ATOM	2112	CE1	TYR	228	6.085	27.801	16.566	1.00	8.20
ATOM	2113	CD2	TYR	228	8.042	26.192	17.667	1.00	2.00
ATOM	2114	CE2	TYR	228	8.397	27.372	17.017	1.00	4.75
ATOM	2115	CZ	TYR	228	7.407	28.171	16.464	1.00	7.14
ATOM	2116	OH	TYR	228	7.726	29.323	15.773	1.00	17.75
ATOM	2117	HH	TYR	228	8.674	29.467	15.777	1.00	0.00
ATOM	2118	C	TYR	228	5.182	22.342	18.535	1.00	5.39
ATOM	2119	O	TYR	228	4.005	22.311	18.874	1.00	8.14
ATOM	2750	C	M32	300	8.267	25.094	7.801	1.00	25.03
ATOM	2751	C1	M32	300	8.858	23.853	7.444	1.00	25.98
ATOM	2752	C2	M32	300	8.379	24.441	10.246	1.00	20.98
ATOM	2753	C3	M32	300	8.980	23.178	9.869	1.00	24.37
ATOM	2754	C4	M32	300	9.212	22.895	8.505	1.00	29.21
ATOM	2755	C5	M32	300	8.010	25.433	9.161	1.00	22.21
ATOM	2756	CL1	M32	300	7.230	26.454	13.601	1.00	25.81
ATOM	2757	C6	M32	300	7.411	26.704	9.530	1.00	19.62
ATOM	2758	C7	M32	300	8.120	24.794	11.600	1.00	21.01
ATOM	2759	C8	M32	300	7.183	26.988	10.884	1.00	18.60
ATOM	2760	C9	M32	300	7.533	26.044	11.925	1.00	19.36
ATOM	2761	S	M32	300	9.015	23.469	5.780	1.00	17.20
ATOM	2762	O	M32	300	9.071	24.779	4.968	1.00	16.38
ATOM	2763	O1	M32	300	10.242	22.582	5.534	1.00	17.25
ATOM	2764	C10	M32	300	5.199	22.312	4.491	1.00	27.00
ATOM	2765	O2	M32	300	4.122	22.777	4.126	1.00	32.92
ATOM	2766	C11	M32	300	6.360	23.283	4.882	1.00	23.85
ATOM	2767	N	M32	300	7.627	22.680	5.299	1.00	22.06
ATOM	2768	C12	M32	300	6.769	20.390	5.043	1.00	32.04
ATOM	2769	C13	M32	300	7.755	20.001	3.914	1.00	39.28
ATOM	2770	O3	M32	300	7.210	19.046	2.977	1.00	47.51
ATOM	2771	C14	M32	300	7.939	18.829	1.852	1.00	48.79
ATOM	2772	C15	M32	300	7.490	21.418	5.984	1.00	25.44
ATOM	2773	N1	M32	300	5.477	20.938	4.593	1.00	29.98
ATOM	2774	C16	M32	300	4.491	19.869	4.670	1.00	30.81
ATOM	2775	C17	M32	300	0.442	15.501	8.992	1.00	49.84
ATOM	2776	N2	M32	300	2.584	18.058	7.186	1.00	41.26
ATOM	2777	C18	M32	300	1.691	17.430	8.145	1.00	44.57
ATOM	2778	C19	M32	300	1.309	16.052	8.031	1.00	46.32
ATOM	2779	C20	M32	300	2.968	19.503	7.333	1.00	38.25
ATOM	2780	C21	M32	300	1.145	18.166	9.257	1.00	43.40
ATOM	2781	C22	M32	300	3.160	17.297	6.016	1.00	39.49
ATOM	2782	C23	M32	300	5.033	19.081	5.868	1.00	36.22
ATOM	2783	O4	M32	300	6.468	19.227	5.792	1.00	37.50
ATOM	2784	C24	M32	300	4.489	19.666	7.202	1.00	33.76
ATOM	2785	N3	M32	300	-0.065	16.209	10.032	1.00	49.11
ATOM	2786	C25	M32	300	0.286	17.511	10.160	1.00	45.71
ATOM	2787	C26	M32	300	4.673	17.567	5.876	1.00	35.53
END									

FIG. 37



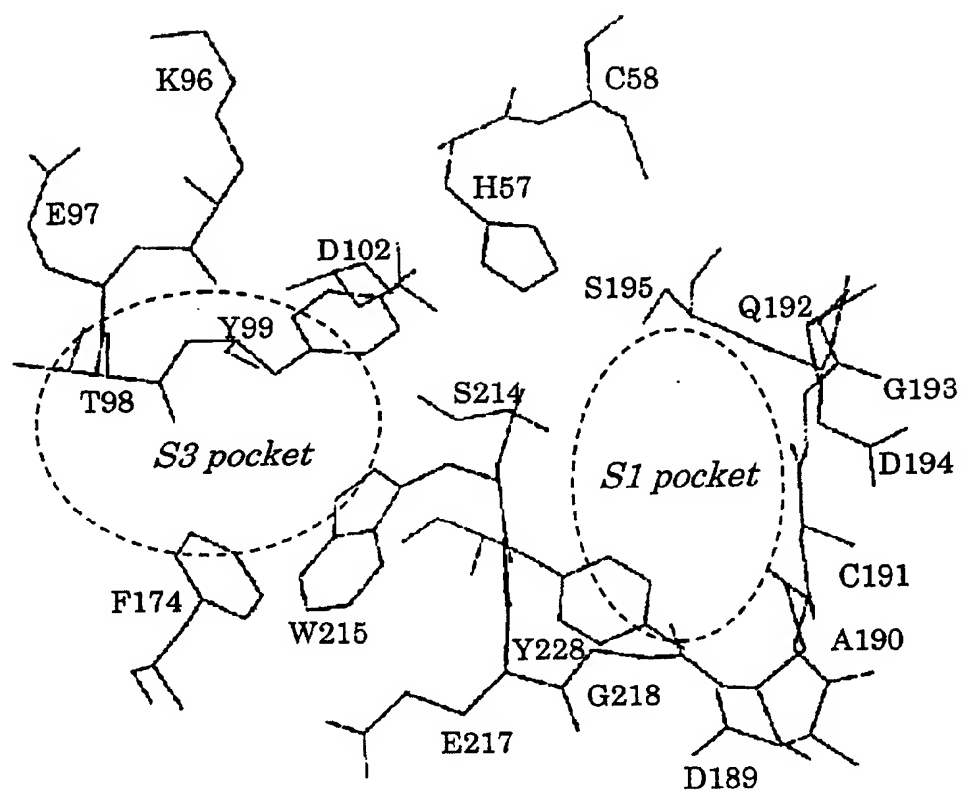
Human Factor Xa (Des-Gla domain)

FIG. 38



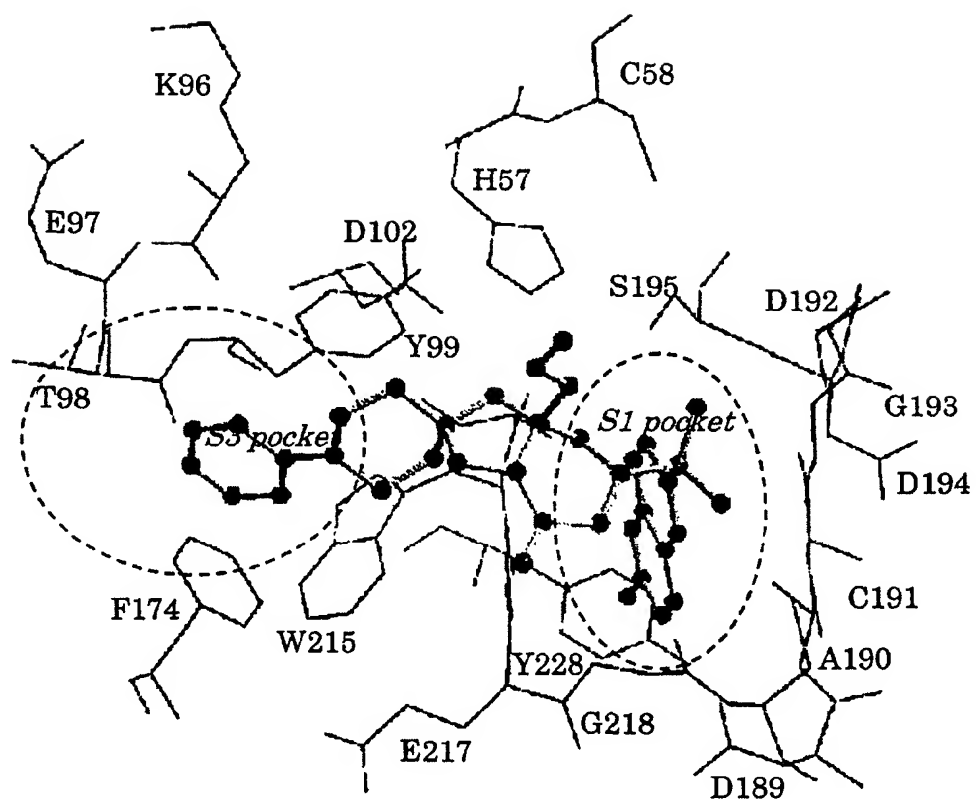
Human Factor Xa (Des-Gla domain) — Compound A

FIG. 39



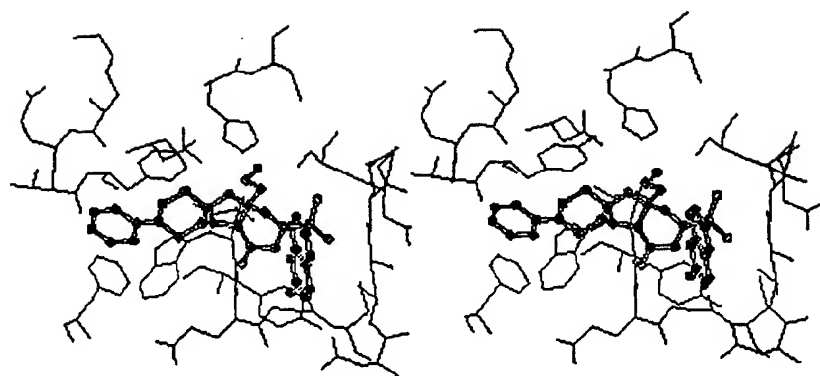
Factor Xa Active Site

FIG. 40



Factor Xa Active Site occupied Compound A

FIG. 41



Stereo View  
Factor Xa Active Site occupied Compound A

FIG. 42

- ① CHYMOTRYPSIN NO. IN 1FAX STRUCTURE  
 ② AMINO ACID SEQUENCE OF THE SERINE PROTEASE DOMAIN IN FXA  
 ③ SERIAL NO. OF THE RESIDUES OF THE SERINE PROTEASE DOMAIN IN FXA

①	②	③	①	②	③	①	②	③	①	②	③	①	②	③
16	ILE	1	67	ARG	53	119	ALA	105	169	LYS	157	220	CYS	209
17	VAL	2	68	VAL	54	120	PRO	106	170	LEU	158	221	ALA	210
18	GLY	3	69	GLY	55	121	ALA	107	171	SER	159	222	ARG	211
19	GLY	4	70	ASP	56	122	CYS	108	172	SER	160	223	LYS	212
20	GLN	5	71	ARG	57	123	LEU	109	173	SER	161	223A	GLY	213
21	GLU	6	72	ASN	58	124	PRO	110	174	PHE	162	224	LYS	214
22	CYS	7	73	THR	59	124A	GLU	111	175	ILE	163	225	TYR	215
23	LYS	8	74	ALA	60	125	ARG	112	176	ILE	164	226	GLY	216
24	ASP	9	75	ALA	61	126	ASP	113	177	THR	165	227	ILE	217
25	GLY	10	76	GLU	62	127	TRP	114	178	GLN	166	228	TYR	218
26	GLU	11	77	GLU	63	128	ALA	115	179	ASN	167	229	THR	219
27	CYS	12	78	GLY	64	129	GLU	116	180	MET	168	230	LYS	220
28	PRO	13	79	GLY	65	130	SER	117	181	PHE	169	231	VAL	221
29	TRP	14	80	GLU	66	131	THR	118	182	CYS	170	232	THR	222
30	GLN	15	81	ALA	67	131A	LEU	119	183	ALA	171	233	ALA	223
31	ALA	16	82	VAL	68	131B	MET	120	184	GLY	172	234	PHE	224
32	LEU	17	83	HIS	69	132	THR	121	185	TYR	173	235	LEU	225
33	LEU	18	84	GLU	70	133	GLN	122	185A	ASP	174	236	LYS	226
34	ILE	19	85	VAL	71	134	LYS	123	185B	THR	175	237	TRP	227
35	ASN	20	86	GLU	72	135	THR	124	186	LYS	176	238	ILE	228
36	GLU	21	87	VAL	73	136	GLY	125	187	GLN	177	239	ASP	229
37	GLU	22	88	VAL	74	137	ILE	126	188	GLU	178	240	ARG	230
38	ASN	23	89	ILE	75	138	VAL	127	189	ASP	179	241	SER	231
39	GLU	24	90	LYS	76	139	SER	128	190	ALA	180	242	MET	232
40	GLY	25	91	HIS	77	140	GLY	129	191	CYS	181	243	LYS	233
41	PHE	26	92	ASN	78	141	PHE	130	192	GLN	182	244	THR	234
42	CYS	27	93	ARG	79	142	GLY	131	193	GLY	183			
43	GLY	28	94	PHE	80	143	ARG	132	194	ASP	184			
44	GLY	29	95	THR	81	144	THR	133	195	SER	185			
45	THR	30	96	LYS	82	145	HIS	134	196	GLY	186			
46	ILE	31	97	GLU	83	147	GLU	135	197	GLY	187			
47	LEU	32	98	THR	84	148	LYS	136	198	PRO	188			
48	SER	33	99	TYR	85	149	GLY	137	199	HIS	189			
49	GLU	34	100	ASP	86	150	ARG	138	200	VAL	190			
50	PHE	35	101	PHE	87	151	GLN	139	201	THR	191			
51	TYR	36	102	ASP	88	152	SER	140	202	ARG	192			
52	ILE	37	103	ILE	89	153	THR	141	203	PHE	193			
53	LEU	38	104	ALA	90	154	ARG	142	204	LYS	194			
54	THR	39	105	VAL	91	155	LEU	143	205	ASP	195			
55	ALA	40	106	LEU	92	156	LYS	144	206	THR	196			
56	ALA	41	107	ARG	93	157	MET	145	207	TYR	197			
57	HIS	42	108	LEU	94	158	LEU	146	208	PHE	198			
58	CYS	43	109	LYS	95	159	GLU	147	209	VAL	199			
59	LEU	44	110	THR	96	160	VAL	148	210	THR	200			
60	TYR	45	111	PRO	97	161	PRO	149	211	GLY	201			
61	GLN	46	112	ILE	98	162	TYR	150	212	ILE	202			
61A	ALA	47	113	THR	99	163	VAL	151	213	VAL	203			
62	LYS	48	114	PHE	100	164	ASP	152	214	SER	204			
63	ARG	49	115	ARG	101	165	ARG	153	215	TRP	205			
64	PHE	50	116	MET	102	166	ASN	154	216	GLY	206			
65	LYS	51	117	ASN	103	167	SER	155	217	GLU	207			
66	VAL	52	118	VAL	104	168	CYS	156	218	GLY	208			

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/04374

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> Int.Cl <sup>7</sup> C07D471/20, 498/10, 498/20, 519/00, A61K31/4985, 31/5377, 31/541, A61P7/02, 9/00, G01N33/50, 33/15, C07M7:00 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) Int.Cl <sup>7</sup> C07D471/20, 498/10, 498/20, 519/00, A61K31/4985, 31/5377, 31/541, A61P7/02, 9/00, G01N33/50, 33/15, C07M7:00 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS (STN), CAOLD (STN), REGISTRY (STN), MEDLINE (STN), BIOSIS (STN)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	Mochalkin, I. et al., 'Structures of thrombin retro-inhibited with SEL2711 and SEL2770 as they relate to factor Xa binding' Acta Crystallogr., Sect. D: Biol. Crystallogr., April 1999, Vol.D55, No.4, pp.785-793	18 1-12
Y A	Maduskuie, T.P. Jr., et al., 'The rational design and synthesis of novel Bis-phenylamidine factor Xa inhibitors' Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11, 1997, MEDI-048	18 1-12
Y A	Wiley, M.R., et al, 'Indole and indazole as neutral S1 binding elements in the design of potent inhibitors of human factor Xa' Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26, 1999, MEDI-026	18 1-12
Y A	Ostrem, J.A., et al., 'Discovery of a Novel, Potent, and Specific Family of Factor Xa Inhibitors via Combinatorial Chemistry' Biochemistry, 1998, Vol.37, No.4, pp.1053-1059	18 1-12
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 21 September, 2000 (21.09.00)		Date of mailing of the international search report 03 October, 2000 (03.10.00)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/04374

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Hauptmann, J. et al., 'Synthetic inhibitors of thrombin and factor Xa: from bench to bedside' Thromb. Res., 1999, Vol. 93, No. 5, pp. 203-241	1-12, 18

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/04374

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15,17  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Claim 15 pertains to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2) (a) (i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search. Claim 17 : see extra sheet
2. ☒ Claims Nos.: 13-17  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
See extra sheet
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Inventions as set forth in claims 1 to 12 pertain to compounds having a specific chemical structure and having an FXa inhibitory activity, medicinal compositions containing the same, a process for producing the same and production intermediates thereof.

On the other hand, inventions as set forth in claims 13 to 18 pertain to compounds inhibiting FXa based on the interaction with the S1 and S3 pockets of FXa and a method for predicting the same.

Although the compounds relating to the former claims inhibit FXa, the technical idea of an invention of a compound resides in the chemical structure thereof per se and is different from the technical idea of the latter claims expressed as the combination of the intensities of the interactions with FXa pockets. In this case, inventions of compounds having no analogy in chemical structures should be understood as belonging to different groups of inventions, even though these compounds are applied to the same diseases. Such being the case, it should be considered that there are at least two groups of inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/04374

Continuation of Box No. I of continuation of first sheet (1)

## Column I. 1. (claim 17)

Inventions as set forth in these claims merely involve a list of properties which should be exhibited by FXa inhibitors. Therefore, no subject of the technical idea but merely information statement is provided therein. Such being the case, these claims relate to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

## Column I. 2. (claims 13 to 17)

Inventions as set forth in claims 13 to 16 pertain to compounds and use thereof. However, these compounds are specified merely depending on the properties. Namely, the chemical structures of these compounds are never specified. Since the technical idea of an invention relating to a compound resides in the chemical structure of the compound per se, the above inventions without any specification of the chemical structure fails to satisfy the definite requirements to such an extent as enabling the International Searching Authority to perform meaningful search. Thus, no search has been carried out under the provisions of Article 17(2)(a)(i) of the PCT.

Claim 17 pertains to a pharmacophore for designing FXa inhibitors. This pharmacophore consists of certain "parameters" and "interactions" caused thereby.

To impart some meaning to a parameter and an interaction, it is usually considered as necessary that the value of the parameter and the intensity and properties of the interaction are specified, or manipulations (analysis, calculation, etc.) concerning the same are specified, as being equivalent to the above specification. In this claim, however, no such specification has been made but it is merely stated vaguely that when an FXa inhibitor exerts its effect, there are some conditions relating to the well known pockets of FXa.

Such being the case, this claim fails to satisfy the definite requirements to such an extent as enabling the International Searching Authority to perform meaningful search. Thus, no search has been carried out under the provisions of Article 17(2)(a)(i) of the PCT.